



Handbook for Cancer Research in Africa



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Foreword

Sub-Saharan Africa (SSA) suffers from a growing cancer burden. By the year 2030, cancer and other non-communicable diseases may overtake some infectious diseases as leading causes of death in SSA. Addressing this burden requires a multi-pronged approach that includes improved policy and funding support, improved knowledge of cancer in SSA, awareness of the cancer burden, clinical oncology infrastructure and improved cancer health systems, and cancer prevention and control strategies. Key to lowering the cancer burden in SSA is the development of cancer research that addresses these issues in the African setting. Just as the development of knowledge about cancer and its prevention and treatment have made major contributions to reducing the cancer burden in the developed world, Africa too must create knowledge that will address African-specific cancer problems for the improved health of Africans.

Realizing this goal, however, will not be easy: it will require building research resources and infrastructure as well as collaborative partnerships across countries and disciplines. It may require new methods and approaches that leverage the unique situation in SSA. It demands that new leadership, critical thinking and investment be aligned with the need to improve knowledge of cancer in SSA. Aside from the challenges, cancer research in SSA also has the potential to provide unique insight into cancer that cannot be attained anywhere else in the world. The example of the unique African contribution to the identification, understanding, and management of Burkitt lymphoma is just one example of how African science can impact cancer globally.

For cancer to be conquered in Africa, and for African scientists to contribute to the global understanding of cancer prevention and control, a new cadre of researchers must be nurtured on the African continent. There are many steps in this process: developing or enhancing research training programs; mentoring researchers through research training at multiple levels; development of research infrastructure including wet and dry laboratory facilities; creating academic tracks within institutions that will allow researchers to work in a setting that is conducive to research; and creating sustainable funding and resource models that will enable capacity for research.

While these goals may not be attained rapidly or easily, this Handbook for Cancer Research in Africa represents one small step in disseminating principles for cancer research to African scientists. The chapters are meant to serve as a guide for those who want to develop or expand careers in research in Africa. Clearly, not all relevant topics can be covered here. The goal of this volume is to provide an introduction for researchers, who may need additional formal training and experience to realize their research goals. This volume may also be of use to those who are in a position to foster research in Africa, including non-African scientists, governmental and non-governmental agencies, and advocacy groups.

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President, African Organization for Research and Training in Cancer (AORTIC)
Summer 2013

Preface

The burden of cancer in Africa is growing as are the costs. In only a few years many countries facing the growing cancer burden will be confronted with unmanageable treatment costs for the disease. The key to lowering the cancer burden in Africa is developing research addressing cancer issues in the African setting. Just as knowledge about cancer and its prevention and treatment has made major contributions to the reduction of its burden in the developed world, Africa too must create knowledge that will address Africa-specific cancer problems for the improved health of Africans.

Cancer research provides the evidence base on which cancer prevention, control and treatment strategies are built. Without research data, it is difficult if not impossible to achieve the goals of appropriate and targeted preventive or treatment strategies, efficient use of the limited health-care resources, and empowerment of people and health-care systems to integrate knowledge of the disease into their behaviour. Developing the skills of cancer researchers and research infrastructure also has the benefit of stimulating educational, social and economic activities, consequently providing wide benefits to society.

This handbook is the first of its kind to address the unique needs and opportunities in sub-Saharan Africa for cancer researchers. By covering the topics fundamental to all cancer research, but from an African perspective, the handbook serves as a tool for investigators at all levels and from many backgrounds to raise the level of cancer research being undertaken in Africa. It is meant to serve as a guide for those who want to develop or expand careers in research in Africa. This handbook may also be of use to those who are in a position to foster research in Africa, including non-African scientists, governmental and nongovernmental agencies and advocacy groups.

The preparation of this handbook could not have been possible without the support of and input from the African Organization for Research and Training in Cancer (AORTIC) and a committed group of people. I applaud the authors for their role in creating this landmark document, which is an important contribution to the ultimate reduction of suffering and death due to cancer in Africa. Special thanks go to Professor Timothy R Rebeck of the University of Pennsylvania, Philadelphia, who was instrumental in guiding this volume from conception to publication. I would also like to recognize my WHO colleagues who contributed to this invaluable work.



Dr Luis G Sambo
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SECTION I: PREPARING TO DO RESEARCH

Chapter 1

Basic research principles

Serigne M Gueye and Timothy R Rebbeck

Chapter outline

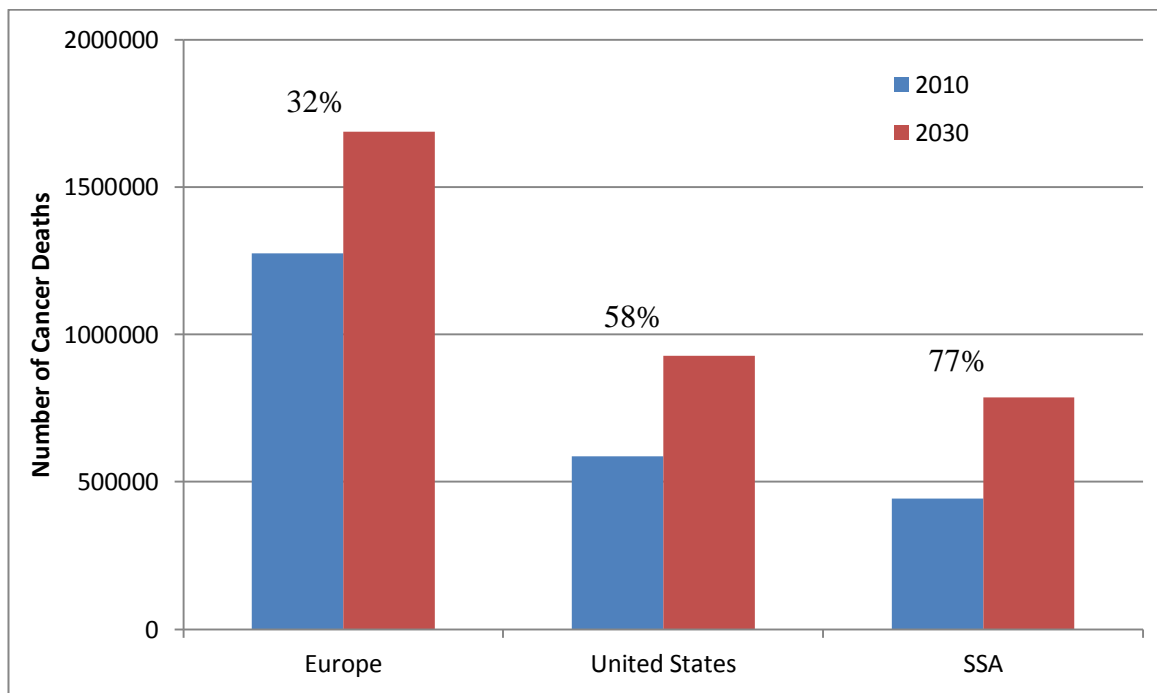
1. Why conduct cancer research in Africa?
2. “Semper aliquid novi Africam adferre” (Africa always brings (us) something new)
3. Is there an “African” approach to cancer research?
4. General principles for cancer research in Africa
5. Summary

1 Why conduct cancer research in Africa?

In 1899 the surgeon Roswell Park predicted that cancer would overtake the common infectious diseases of the time as a killer of Americans. At that time people would not believe that this was realistic, but in less than 30 years of this prediction cancer was second only to heart disease as a cause of American deaths. We see the same trend in Africa today. Figure 1 presents the expected growth of the cancer burden in sub-Saharan Africa between 2010 and 2030 compared with Europe and the United States. These data show that the number of deaths due to cancer will increase in sub-Saharan Africa at a substantially greater rate than in Europe or USA. There is evidence also that cancer incidence and mortality are vastly underreported,⁽¹⁾ so cancer deaths in Africa are likely to be higher than shown in Figure 1.

Along with the big increase in cancer, Africa continues to face a crisis in communicable diseases. There is evidence of substantial decreases in some communicable diseases such as malaria,⁽²⁾ and at some point in the next 20 years cancer will likely overtake certain communicable diseases as a leading cause of morbidity and mortality in Africa. In 2005 the World Bank estimated that chronic diseases were responsible for nearly as many deaths as communicable diseases, and in lower middle income countries chronic diseases were responsible for the majority of deaths. The proportion of deaths due to chronic diseases will increase while deaths from communicable diseases will fall by 2030.⁽³⁾ While chronic diseases, including cancer, are a growing threat to the health of Africans, communicable diseases will not disappear, and health policy- and decision-makers on the continent will have to make important choices to about how to use of the limited resources to improve the health of their populations.

Figure 1: Predicted cancer deaths for 2010 and 2030 as a share of total deaths



There are a number of reasons to promote cancer research as an important activity in Africa:

- The allocation of health-care resources in the African setting requires data to optimally implement cancer prevention and care strategies.
- Building a foundation of Africa-specific knowledge lays the groundwork for translation of the knowledge into important clinical and public-health activities.

The data required to make informed decisions need to include accurate knowledge of cancer incidence and mortality rates, prevention options for specific cancers, and distribution of different types and subtypes of cancer. This will to optimize staffing and procurement of drugs and devices and to employ appropriate strategies and ensure their cost-effectiveness in the context of a specific health system.

Research in the African setting is required for each of these goals to be achieved.

Research in Africa will also provide opportunities for capacity building in a variety of other sectors by increasing educational opportunities, developing infrastructure and improving self-reliance on African solutions for African problems. As Dr Wangari Maathai, founder of the Green Belt Movement and winner of the Nobel Peace Prize, noted that development of resources within Africa is problematic when African governments and individuals are not active partners in development; aid as opposed to home-grown capacity building can induce a culture of dependency; and a crisis mentality towards disease, such as may be engendered by emergency medical aid from abroad, may emphasize immediate results over long-term prevention.⁽⁴⁾ Africa-initiated and Africa-led research can provide accountability for and ownership of the research work.

What can Africa expect from African cancer research? The benefits include improved research infrastructure, a trained workforce, improved clinical capacity and data that have impact on the health of the local population. Each of these is critical for improvement of health in Africa.

2. “Semper aliquid novi Africam adferre”⁽⁵⁾ (Africa always brings (us) something new)

In addition to improving the health of Africans, conducting research in Africa holds the potential to inform the basic science of cancer and cancer prevention and care globally. There are precedents to the critical role Africans in Africa can play in contributing to knowledge on cancer. Excellent African-based research on Burkitt’s lymphoma, an entity first described by Dennis Burkitt, a British surgeon at the Mulago Hospital of Makerere University in Uganda,^(6,7) contributed to the understanding of that disease. The RAJI lymphoblastoid (Burkitt’s lymphoma) cell line was identified by Dr BO Osunkoya⁽³⁾ of the Department of Pathology at the University of Ibadan. This cell line has for many years been distributed worldwide and has played a pivotal role in the understanding of the role of EBV in carcinogenesis and lymphoma. Furthermore, the uniqueness in manifestation and natural history of cancer in Africa might provide insights about the disease etiology and prevention that cannot be found anywhere else. Thus, Africa has the potential to advance the knowledge of cancer in a variety of ways.

3. Is there an “African” approach to cancer research?

Dr Maathai, herself a cancer victim, noted that the traditional African stool is composed of a seat and three legs⁽⁴⁾:

The first leg represents democratic space, where rights—whether human, women’s, children’s or environmental—are respected. The second leg symbolizes the sustainable and accountable management of natural resources both for those living today and for those in the future, in a manner that is just and fair, including for people on the margins of society. The third leg stands for what I term ‘cultures of peace’. These take the form of fairness, respect, compassion, forgiveness, recompense and justice.

Just as the African stool is made out of a single block of wood, each leg, or pillar, is reinforced by others and formed from the same grain, so the issues must be addressed together and simultaneously.

The idea expressed in Dr Maathai’s words provides a framework around which cancer research can be undertaken in Africa. Research can form the basis around which the society can provide for the fundamental rights of human health and well-being and serve as a sustainable and evidence-based foundation for the use of the limited health-care resources and provision of health services to the population, leading to an improved capacity to attain a “culture of peace”.

Each of these points recognizes the imperative that research for improved health of Africans be initiated and led by Africans. Dr Maathai asks: “Why should it take foreign experts working for foreign development agencies and funded by foreign donors to convince the majority of Africans that they should take the problems of deadly but preventable diseases seriously?”⁽⁴⁾ She further observes that for diseases like malaria “... we see a crisis mentality that colors much development assistance, as opposed to putting a priority on prevention, strengthening health systems, and implementing policies to improve the basic health of Africans, which would make them more resilient in the face of preventable yet debilitating illness”.⁽⁴⁾ Given the pending cancer epidemic in Africa, these words demand that Africans take charge of the burden of cancer on the continent and use research at all levels to facilitate the appropriate and efficient use of the limited health-care resources.

4. General principles for cancer research in Africa

The process of knowledge building is not fundamentally different in Africa than in other parts of the world but the specific requirements for building a knowledge base may be unique. Knowledge generation for cancer may involve a series of steps:

- **Cancer enumeration:** Accurate enumeration of cancer incidence and mortality helps to define the scope of the public health and clinical problem and identify the needs for cancer control. As stated in the book, *The emperor of all maladies*, "... science begins with counting. To understand a phenomenon, a scientist must first describe it. To describe it objectively, he must first measure it".⁽⁸⁾
- **Descriptive and analytical epidemiology:** After enumeration of counts and rates, research must be undertaken that characterizes the distribution and determinants of cancer in the population at hand. This includes identifying (ideally, modifiable) factors that cause cancers to arise and, in so doing, identifying the means by which cancer can be controlled.
- **Mechanism explanation:** Epidemiological studies might characterize the causes of cancer, and this information might be sufficient to identify at-risk individuals and propose preventive strategies, but fundamental science is required to explain the mechanism of these associations and to provide insights that might lead to new treatments, including drugs.
- **Translation:** Epidemiological and basic science knowledge has value to the population only if it can be translated into clinically meaningful investigations that can lead to prevention or cure of a disease. Translational science must then be undertaken that leads to the development and testing of new interventions, such as drugs and devices, and preventive strategies in at-risk populations. Clinical and behavioural trials are a central part of this process.
- **Implementation and evaluation:** The strategies developed from basic science and epidemiological studies must be implemented in clinical practice and public-health systems and policy. Implementation science provides a framework for this work and should include analysis of feasibility and cost-effectiveness as well as ongoing evaluation of programmes and strategies.

An investigator considering a research project has many factors to evaluate and questions to ask for each step of the process before beginning the research:

- (a) **Define the research question:** Questions are important if they contribute to the betterment of the health of your community and elucidate questions of interest to the cancer community globally. When considering the research question think about not only the immediate project but also where the research can go in the future.
- (b) **Identify the appropriate study design:** What individuals or organisms should be studied to answer the research question? What design—clinical trial, case-control study or cohort study—is needed to answer the question?
- (c) **Ensure that ethical issues are properly considered:** Are approvals required for human or animal subjects, and if so, what is the process by which they are granted?
- (d) **Develop or implement appropriate measurement tools:** The metrics to be used must be consistent with the question at hand. Sometimes development, and possibly validation, of the metric is required. Such measurements might include questionnaires or laboratory assays.
- (e) **Determine the appropriate statistical analysis approach:** What do you need to do to convince others that the results are meaningful?
- (f) **Disseminate the research:** How are others going to evaluate and learn from your work?

For cancer research in the African setting, additional considerations may be required to make sure the research can be implemented locally. This is particularly important in settings without substantial research experience. Some of these considerations are relevant to a variety of undertakings in Africa not just cancer research:⁽⁹⁾

- (a) Success metrics: Tie research to goals, and timeline to a finite end-point.
- (b) Institutional buy-in: Require a local institution to partner in or sponsor the research or a researcher. This may require incentives or agreements to ensure the institution will adequately support the research.
- (c) Leverage existing resources: In many parts of Africa, research resources and infrastructure are already in place. Leveraging existing resources rather than starting to develop new ones is important.
- (d) Governance: Seek active involvement of key stakeholders in the research institution administration to ensure governance over research resources and infrastructure is adequate.
- (e) Supply chain and procurement: Negotiate for access to required reagents and supplies beyond existing agreements.
- (f) Staffing continuity: Work towards a structure that allows funded and trained individuals to stay in a position to lead the work for the required period.
- (g) Absorptive capacity: Avoid bottlenecks in research flow by providing support in stages and over a long period so that the system has the time to build appropriate workforce, infrastructure and other key resources.

5. Summary

Cancer represents an important and growing challenge in the health of Africans, but cancer research in Africa remains in its infancy. Substantial investment and development are required to address these needs. It is critical to develop an approach to cancer research and the translation of research results that will optimally address the needs of African populations.

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Chapter 2

Research career considerations

Glenn Jones, Nathan Jones, Trishala Menon, Nina Mazze and Tina Madzima

Chapter outline

1. Introduction
2. Why do research?
3. Are you a fit for research?
4. How do you begin your research career?
5. How do you sustain your research career?
6. How will you evaluate success?
7. Summary

1. Introduction

This chapter deals with the factors to take into account if you are considering doing research or pursuing a research career. There are many types of research and research positions, so one chapter cannot possibly deal with all the relevant aspects. Other chapters in the handbook focus on types of research, data management, partnerships and networking, leadership and mentoring, funding, and documentation of progress. We deal with a strategic, critical gap; that of the low numbers of investigators involved in front-line clinical research, where key local evidence about the quality of care and how that is evolving must be obtained. This chapter looks at why we need research, how to approach a personal decision to do research and how to begin, sustain and evaluate your research career.

2. Why do research?

Since the Age of Enlightenment in Europe and America, the primary objective of western medicine has been to improve well-being and reduce suffering of people through greater empiricism.⁽¹⁾ The most important objectives of clinical research are three: to prove that the care provided is the right care and of the best quality, to improve care quality from an up-to-date to a state-of-the-art status, and to advance and transform care quality by innovation. The logical flow of effort goes from identifying unknowns to designing studies, capturing data and their contexts, and sharing knowledge and applying it wisely for human benefit. To this linear flow may be added dynamic recursive loops of iterations that enable optimization of the quality of care and evaluation of disruptive innovations. Biomedical research is typically quantitative as it focuses on classification and measurement of causal relationships and their modifiers.⁽²⁾ Such research can be expensive and slow, but well-designed cohort studies, randomized trials and large registries are generating results with worldwide impact. Evidence-generating research can inform, and may sometimes directly determine, patient decisions.

Empiricism and evidence-based medicine (EBM) have been perceived by some people in the low- and middle-income countries as inherently “western” in origin and nature or as an expensive luxury.⁽³⁾ We see some truth in this view. Some proponents of EBM make strong assumptions that evidence is always externally generalizing when drawn from randomized trials or meta-analyses.⁽⁴⁾ More to the point is that local and

regional research findings are sorely needed in low- and middle-income countries, including all of Africa. Local data answering questions of immediate relevance are almost always better than data from a study or trial from afar, done in foreign populations, and possibly with unfamiliar technologies or with outcome measures that may depend on the context, culture or language. A mature theory of medical choice⁽⁵⁾ does not require uniformity of clinical practice around the world; it is responsive to the context. However, it does require no-nonsense handling of research, local or otherwise. It seeks informed choice by patients and real consent relevant to individual predicaments.⁽⁶⁾

We believe that the opportunity for research into cancer in Africa is truly immense. Given the changes in cancer incidence and the less-than-desirable pace of adopting newer technologies such as the use of radiation equipment or planning methods, there presently are tremendous pathologic, clinical and treatment heterogeneities in low- and middle-income countries. Diversity constitutes a rich resource for research into statistical associations and causality, to explore how local factors are relevant and how one may best implement change to optimize the quality of care. Most questions that could be asked in cancer management can be studied in Africa today or in the near future.

Front-line clinicians such as nurses, therapists, physicists, social workers, nutritionists, physicians and others generate on a daily basis impressive quantities of data about their patients. If data collection could occur seamlessly during routine clinical practice, these data would be of greater quantity and higher quality than those collected over short study periods. They would come at lower cost, which could be reduced even further if the data are handled electronically. Therefore, resource limitations in Africa do not preclude doing a large volume of clinical research. Studies typically require more of investigators' time than academic infrastructure. Clinicians can be organized, intentional and systematic in their approach to data, research and providing quality care. Every clinician can be part of a flow of data that addresses relevant questions in his or her practice. Data from clinical practice and add-on studies or trials must be translated into practice assets^(7,8) and assets for the health-care system and the larger enterprise of research, as publications or spin-off research projects. Different varieties of front-line clinical research are necessary to document and advance the quality of care within the local practice. This kind of research is central in evidence-based medicine⁽²⁾ and is characteristic of the work of competent clinicians.⁽⁹⁾

3. Are you a fit for research?

The decision to do research or to have a full research career is very personal. Interest and abilities may be more important than opportunity and environment, as opportunities can sometimes be generated and environmental contexts can change. Before committing to research, you need to exercise imagination and evaluate your fit for research for your current and future situations.

First, you have to "know yourself". Assess your philosophy, motivations, capacities, efficacy, vision, and personality as they relate to research work and other undertakings in which you could spend your time. Your philosophy includes your worldview and opinion in questions such as what is? what can I know? what should I do? what can be changed? how does change occur? who is responsible for change? Research is only possible with certain types of answers to these questions. Your answers will help you to define what you mean by quality of health care. A high level of motivation is needed in research to get through rough times, disappointments, setbacks and conflicts. Special personal experiences like previous exposure to cancer or research help, but you need real passion to sustain your research. The capacity to do good research depends on your training and skills or knowledge. You should be able to see yourself as a researcher over time, to visualize your success and to see yourself contributing to your profession and community. You should map how your research will relate to your professional competencies.⁽⁹⁾ In relation to personality, a good researcher has innate curiosity and likes discovery. Gifted individuals frequently ask how things can be made better and frequently suggest improvements. A good researcher also needs to be comfortable with uncertainty, because often analyses may be inconclusive or of limited interpretation or applicability. Overall,

your worldview and motivators will shape your research vision while your capacity for hard work will influence your pace of work, its accuracy and impact.

Second, you have to know your environment. There are many barriers to conducting good research, including insufficient time to gain essential knowledge and skills; inadequate mentoring, collaboration, resources, staffing, equipment and materials; limited access to patients and their data; obstruction from clinical colleagues to do research; little personal, team or institutional governance and administration support to organize research; and short, unrealistic timelines that leave zero margin for error, chance or contingency.⁽¹⁰⁾ Do not be put off by myths about who can do good research. Infrastructure limitation is not always a barrier to research because an investigator could work alone in some cases, and some small studies need little or no infrastructure. Also, training limitations and experience should not be a barrier because you can expand your capacity for research simply and rapidly by doing research and learning “in-context”.⁽¹¹⁾ You can take part-time and online courses and read research literature and work with data sets from the studies reported in the literature.

Third, your personal analysis should include a temporal perspective. This involves setting up contingencies for your personal life activities including retirement. How long you are going to commit to research has to match the time horizons of your projects, your research arc, your career and your life. You have to decide whether you will be a good fit for research as you get older or grow in your career. Most important, you need to be sure that your research and its environment will support your authentic self, that they will not erode your integrity, professionalism or ethics.

Choosing between an entirely clinical path and a path in which research will be a component among others constitutes what may be an irreversible decision. And the process of making this decision is “economic” in nature, meaning that there are opportunity costs to be considered. The cost of committing to one path may be that you cannot go the other way after some time owing to changes in your environment or life and family. If you conclude that you have a personal fit for the sole research path then you should be able to identify the “grain” from that. If you can anticipate personal safety with steady progress in your work, then you may be willing to pay direct and opportunity costs to be a researcher and to realize the full set of gains from your ideas and data. If your assessment is accurate, you will be making an informed decision to become a researcher.

4. How do you begin your research career?

Rather than commence research with a bare or hyper-lean plan,⁽¹²⁾ we suggest that you spend time addressing several strategic themes by writing a multipage draft plan. Set out reasonable goals, define your team and resources, analyse your time requirements and schedule for them, describe the surrounding governance and administrative structures for your research, and determine how you will handle funding and academia factors.

First, set goals with timelines. Goals for you and your career may be shaped by published lists of research objectives and required competencies.⁽⁹⁾ Short-term goals may include learning through self-directed, in-context or network opportunities⁽¹³⁾ or formal courses, programmes and certification training. These will prepare you for a more academic career. If you are a clinician, dealing with a large number of patients over a short period will expose you to a variety of situations that can advance your expertise in diseases and treatments. This is an essential element for many research undertakings. As you begin research you might choose opportunistic studies that are smaller, simpler and quicker to complete. Rapid study completion and publication are possible if you conduct research where patients are ample, you select new methods or technologies being introduced where you work, and you seek easy-to-measure heterogeneities, where statistical power is high.

Second, determine the resources you need and mobilize and direct them to your research and career. Access to a sufficient flow of patients is mandatory. Your time is another critical resource. You need to be efficient in all your work and to carve out quasi-protected periods of time to focus on your research. Avoid focus-disrupting, random task switching between clinical and research activities and reduce the number of planned switches per day and week. Do not reinvent anything that already works well for others and that you can appropriate. Draw from available literature and books, research forms and processes and learn from other researchers, your supervisors and mentors. Be analytically ruthless and realistic when projecting the time a study will take over its full arc from idea generation to writing of papers. Even small studies such as a retrospective cohort analysis of prognostic factors for survival can take 50 to 250 hours. A prospective survey of a 100 patients might take 400 to 800 hours. Always have at least two questions to be answered by a study. The extra effort required for that is slight but the results, such as the number of products and future extensions of your work, will be multiplied.

Third, determine with whom you will work. Consider colleagues and allied staff, hospital volunteers, students and interns doing research courses for credit. Once you define your team, you have to optimize its performance and sustainability. Typical issues of group dynamics, organization and management need to be dealt with.⁽¹⁴⁾ Learn how to lead your team. Obtaining the right people for your team, sharing your vision and tasks, coordinating efforts and supervising delegated activities are priorities and will take some of your time. But bringing together those with the necessary skills, knowledge and time can advance your research and career quickly and to high levels. People are “force multipliers” who effectively increase available time-on-task, and from small studies without large grant funding, with the right team you can conduct a larger study, accelerate one to completion, or carry out several studies in parallel. You may decide to go it alone as a research entrepreneur or act as an “entrepeneur” within an organization.⁽¹⁵⁾ As a one-person research team you will control and be responsible for all aspects of your research. This may give you greater control over ideas, methods, timing, data quality and generated assets.

Fourth, you have to orient yourself with formal funding and academia requirements. As a reasonable simplification, your choice will fall along one dimension that has the minimalist approach at one end and the maximalist approach at the other end. Research using the minimalist approach can be less expensive as it is conducted with a limited surrounding structure, it can be of limited risk to patients, focus more directly on patient care, and be of short duration. These attributes would fit a researcher in the entrepreneurial-intrapreneurial mode or a small research team. Its agility is perfect in focusing on the local quality of health care by improving it with local data, in-clinic translational studies to optimize care or technologies, health services research and economic analyses, and psychosocial or supportive care studies such as those for validating measurement tools. It allows flexibility, deeper knowledge of your own data and satisfaction from realizing incremental changes to clinical policies and procedures. In contrast to the minimalist approach, the maximalist approach can be expensive; requires a lot of surrounding structure associated with academia, granting agencies and formal trials groups; poses greater risks to patients; focuses more on disruptive technological and clinical changes; and is of long duration. This mode is essential for basic science research and definitive clinical trials. It confers extra credibility and generates greater resources and more opportunities for promotion and tenure. Very few clinicians or even full-time researchers can work at this end of the spectrum: opportunities are limited, more formal education requirements have to be met, obtaining research grants can be time consuming and success is not assured. Successful academic researchers spend much of their time acting like CEOs—working the system, writing grants, editing papers and reports, participating in committees, trying to commercialize the research products, and so on. We do need researchers at that level, who can bring together requisite staffing resources and massive multiyear grants. This will allow tackling of big projects and the great challenges of our time. However, most individuals interested in research will never become such giants, nor should they aspire to be such.

Regarding funding and academia, academic units, universities, trials groups and granting agencies overly focus on those who are just starting out or those who are well established. The academia want someone to

get into a career as early as possible. The grace period for being a “young investigator” is generally only five to seven years, ten at the most, from initial work or academic appointment. Some grant awards are available only to real neophytes, so you would have to start dealing with funding organizations early. Other grants tend to go to those who are established in universities or research units and who already have a track record with grants. The bottom line is that should you chose to enter research slowly or tentatively but without interest in grants or academic appointments, you will likely have difficulty later obtaining an academic position or grants. If your long-term research objectives require large-scale, sustained support, then you almost certainly have to jump into an academic track right at the beginning of your career.

Certainly there is a balanced approach lying between the minimalist and maximalist orientations. Beginning as minimalists, some researchers go on to develop significant teams to conduct thousands of hours of research each year, with slightly irregular and mostly soft funding from sources such as public charities, individual donors, pharmaceutical companies, unrestricted education and research funds, endowments and estates. A solid researcher using this middle-of-the-road approach is hard to find at present, and we believe that they are needed in large numbers. Recent changes in funding emphasis, for example the emerging grants for translational research and knowledge transfer, team awards that must include clinical areas, network and consortium grants and the like, suggest that the academic structure of formal research may be changing. A solid cadre of pioneering, networking, intermediate-level researchers working where there is little academic infrastructure, as is the case in most parts of Africa, would be a significant force in its own right, while it would also provide a bridge to the development of more high-level infrastructure.

Fifth, you need to work within, or should put together, some form of infrastructure consisting of appropriate governance, administrative and data-management systems.⁽¹⁶⁾ You have to have at least two types of such infrastructure, one for your career and one for your research. These are critical to succeed, but you should aim for lean or streamlined systems to minimize their draw on your time and resources. Governance is concerned with being able to make a business case for your career and your research, explaining how your plans and data can be assets for you and your organization and how they are aligned with outside requirements of ethics, regulations pertaining to privacy or security, and funding rules and agencies.⁽⁷⁾ Be explicit about where, when and how efficiencies, effectiveness and success are going to be measured. On your career side, you should document with supporting data how you spend your time. Compile reference lists, track your ideas as they evolve and keep your curriculum vitae updated. Even small studies should have a governance, administration and data-management frame. If you have several studies or projects, look at how they can share methods. This kind of parallelism produces cross-project coherence, efficiencies and synergies. Standardize questionnaires, data forms, and data-capture and management processes across all your studies.⁽¹⁷⁾ Your administrative functions will project your governance plan in and across your studies and projects, fostering pooling of data maps; use of standardized policies, procedures and materials such as forms and variables; ensuring attention to keep the research substrates useful, for example the software upgrades; and ensuring safety and security of your data, for example by limiting access to files and enforcing compliance with ethics. Professional data management starts from when you are preparing to capture data through to assembling of final cleaned files for definitive statistical analyses.⁽⁷⁾ If you are on an academic track, make sure you understand the governance, administrative and professional data management and analyses infrastructure that you have access to and use it wisely.

5. How do you sustain your research career?

To sustain your research efforts you must ensure a great work-life balance. Directly manage the “economy”—the complexities and dynamics—of your projects and activities.

Be sure to pay attention to how you manage yourself. Project a positive vision and the big picture. Nurture and reflect on your motivations. Develop your plans and curriculum vitae as living or dynamic documents, meaning that you continually update them to be current and to keep your research focused. Exercise

personal discipline to stay on the task and adhere to timelines. Keep a short to-do list and periodically hold “kill-it” sessions for unproductive projects and methods. Build into your projects strategic reviews at pre-set time points. Say “no” regularly to new projects so that your workload is manageable. Compartmentalize work and design your schedule for both efficiency and effectiveness. Minimize task switching between clinical service and research because clinical demands will always trump research plans. Further, manage emails and disruptions from other electronic communication by attending to them at scheduled times. Work to reduce your risk of burnout and to improve work engagement. Positive work engagement consists of high energy, positive emotion and obvious efficacy⁽¹⁸⁾ as opposed to cynicism, ineffectiveness, disengagement, emotional exhaustion and frustration. The most important factors are organizational not personal issues. Ensure your work pace and intensity are reasonable and that you exercise some control over your work and work flow. Work to ensure you obtain adequate rewards for your efforts, have a sense of community and team, promote fairness and align your work with your values.⁽¹⁹⁾

In managing others you will need a true management approach, and business literature is a great resource for this. A real risk is that intervening personnel may filter what you hear or what you impart on others. Problems might develop in data quality or in relationships and you might fail to identify these early enough to make easy corrections. It is recommended that you set up simple measures and rules for workers so that they can make corrections as they enter or work with data and to identify issues that really must come to you. As your team grows to accommodate several workers it morphs into an organization, and this might pose the challenges of drift, disintegration, conflict and chaos.⁽²⁰⁾ Leading will require 5 to 15% of your time for casting the vision, holding meetings, resolving conflicts, fostering relationships, encouraging others and developing people.⁽²¹⁾ Avoid office politics and gossip. Working with paid staff will add budget and human resource concerns.

6. How do you evaluate success?

If you can sustain your research efforts and conclude several projects or cycles of research, you can evaluate your progress and success on the criteria of coping skills, product generation, recognition and agility.

Coping skills deal with how well you are managing yourself, your work and work-life conflicts. You should not be overwhelmed with distress such as emotional or negatively charged stress, be burning out, feeling overwhelmed or becoming depressed. Ensure the compromises you make do not undermine your professionalism, ethics, authenticity, influence or relationships. Small concessions along the way can result in warping of your thinking, behaviour and the overall trajectory, so pay attention to the implications of decisions as you make them and follow up on them. Your objectives are to become ever more professional, authentic and influential. Your mentors can provide external validation of your success. Their evaluations should be positive, encouraging and accurate.

Products from your research should accumulate at a reasonable pace. Such products include well-established methods, infrastructure, theories, personal communications, publications and meta-products such as tools for clinicians and other researchers. You should be fulfilling the typical metrics of academic strength; for example, some of your publications should be well placed in the literature.

Recognition can be seen through a four-fold perspective encompassing internal, external, informal and formal recognition. Develop an explicit communications plan for yourself and your research. Use the new electronic communication methods including web and self-publishing. Your clinical peers should begin to identify you as a local scholar, statistician or researcher. They may refer decision-making to you or seek your advice on literature or their own research. You could become a reliable go-to person when things need doing and when you have proven your expertise. But be clear on what you will do and say “no” enough times to preserve your focus and agility. More formal acknowledgements may come in the form of secured, protected time for research, change in remuneration, improved performance evaluation, or greater scope in your job or

resources to assist your work. You may be promoted, for example from a data worker to a data manager or from a researcher to the head of a research team or unit. If you are on the academic track, university promotions will occur from assistant professor going through the ranks to full professor. External recognition will come through citation of your publications, achieving wide influence in your field, becoming an effective advocate for change, being invited as a participant or presenter at scientific meetings, winning prize awards, gaining media attention, being made a clinician scientist, being appointed to advisory boards and national panels, signing book deals, selling many copies of your books, and so on. Be careful to ensure you are saying “yes” to only what makes sense to you, your team and your mentors.

Agility is another measure of success. Little agility is a liability. If you are able to bring your humanity and work dimensions together successfully, or even synergistically, and you are comfortably more than just technically and economically efficient, you will be able to plan, keep up with change and be ready to seize the excellent opportunities that come up. You will also be able to counteract unforeseen events and to activate contingency plans to offset setbacks. Agility for you should include being free enough to relocate if that is in your best interest. When appropriate or desirable, you should be able to stop your research career and retire when you want or need to, for example for health or family reasons.

7. Summary

In this chapter, we address the purposes and structure of clinical research and the dynamics of a research career. We aim is to motivate and guide our readers to take up research or even research careers. Every clinician should display curiosity and interest in the structures, processes and outcomes of health care (22). Most clinicians can be more systematic in their observation and measurement of illnesses to address unknowns and improve care provision. Each can help those doing research or lead research, and some clinicians can lead large-scale research units and departments.

We appeal to all new graduates and established, practising clinicians to seriously consider doing some level of research. But you should not commence research unless your self-analysis indicates that you have a good fit for research in your environment. You have to be willing to pursue what you consider the benefits from your chosen research direction, recognizing the opportunity costs.

Your early research career will be somewhat mechanical—setting goals, building a team, securing your time, establishing appropriate governance and administrative structures and bringing in force multipliers. The most time-critical factor affects the beginning of your research career and has to do whether or not you want to seek grant funding and become an academic researcher. Most researchers will not have full academic roles, especially clinical researchers.

Research is a complex human activity that is difficult to evaluate. It provides amazing answers and generates new, exciting questions. Health caregivers and patients should strive for better health decisions and living, and research that influences these decisions is worth doing. Real success is seeing your well-being, that of those you know well and patients improving in response to your research. The care of patients in Africa and around the world can be improved most quickly through relevant research and greater evidence-based advocacy.

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Chapter 3

Developing and maintaining effective North–South, South–South and South–South–North partnerships

D Cristina Stefan and Ted Trimble

Chapter outline

1. Introduction
2. Pitfalls and tribulations of North-South research collaboration initiatives
3. Principles for successful North–South scientific collaboration
4. Successful North-South research partnerships in Africa
5. The state of South–South research partnerships in Africa
6. Conclusion

1. Introduction

Most economies on the African continent fall under the low- and middle-income per capita categories. The resources they allocate to health research are scarce, and private investment also is modest. With regard to scientific capability, in 2002 only South Africa was ranked among the “scientifically proficient countries”, while Egypt was considered “a scientifically developing country”. All the other countries on the continent were considered “scientifically lagging”.⁽¹⁾

In contrast, the continent’s burden of disease is massive, exemplified by the extent of malaria, tuberculosis, malnutrition and AIDS. Although emancipated from colonialism, African nations maintain complex economic, scientific and cultural relationships with their former colonizing countries. After liberation, African countries had few options and had to resort to relying on the research capacity of these resource-rich countries and to use funds made available by them to address some of the more pressing health issues in Africa. This was aided by what is referred to as the “post-colonial syndrome”, a feeling of collective guilt in the previous colonial powers. Moreover, the process of globalization has eliminated restriction of diseases to particular geographical areas. To give just one example, sickle cell anaemia, mostly seen in the past in African regions with endemic malaria, has become a health-care concern also in the United Kingdom, the United States and Brazil with migration of Africans. Such changes called for health research investment with a global perspective.

Gradually, research collaboration between resource-rich countries, collectively identified as the “North”, and the developing countries forming the “South” progressed from the situation where northern research institutions addressed southern research problems to where northern countries established research capacity in the partner southern countries, and eventually to a state of more equal partnership. In addition, there has been growing appreciation among governments in the North and the South about the importance of health research. The Bamako Call to Action on Research for Health from the Global Ministerial Forum on Research for Health in November 2008 recommended that countries devote at least 2% of their health budgets to research, that donors earmark 5% of their budgets for research and that all countries work to strengthen capacity for research.

2. Pitfalls and tribulations in North–South research collaboration initiatives

While the ultimate goal of North–South research collaboration is to establish strong independent research entities in the South, the road leading to this goal has often been rocky and winding. Some of the patterns of relationship between the partner research institutions have been criticized as “semi-colonial”.⁽²⁾ Among these is the “postal research” model, where the contribution of the southern partner is mostly limited to sourcing and dispatching biological samples for analysis in the North. Another model, “parachute research”, consists of sending a researcher from the northern institution to the southern site for a short time, mainly to collect biological samples and clinical data to be taken to the North for analysis. The “annexed site” is a more evolved model, where the research done by the southern team is directed by northern expatriates. This was seen as a way of ensuring a better quality output and may have included training for local academics. The annexed site model was criticized because a substantial part of the budget was used for the big salaries of the expatriate cadres. It was also argued that because local participating academics earned much bigger salaries than those paid in their own institutions, they were motivated to seek permanent employment with the northern partner. Ultimately, there may be very little benefit for the southern institution in terms of research infrastructure, personnel retention or sustained independent research activity.⁽²⁾

Choice of research questions

With their pervasive health-care demands, African countries must undertake research capable of guiding health policies and improving health outcomes. And since only 10% of the research funds are spent on those diseases that form 90% of the global disease burden,⁽³⁾ the answers to African health problems are not going to be found anywhere else: Africans have to provide them. An analysis of North–South research collaboration projects shows that in the annexed site model, priority was often given to clinical trials of new interventions that were of little relevance for the pertinent country’s health policies. This tendency is less prevalent when the southern collaborators participate in planning the research and in writing the grant proposal. Moreover, the choice of the research theme may be determined in conjunction with the southern country’s health authorities to ensure that the output will be incorporated into policy and so contribute to improve the health status of the population.^(4,5)

The language issue

English, French and Portuguese are spoken by large populations across Africa though not as a first language. Language has largely governed the choice of international research partnerships, with francophone countries preferring France and anglophones the United Kingdom and the United States. Portugal and Brazil are forging close relationships with the Portuguese-speaking African countries. The use of a common language facilitates training of researchers and other research personnel by the North and allows for efficient communication among partners in the team.

Big challenges are encountered in collaborative research situations when drawing up the research instruments such as data collection sheets, questionnaires and informed consent forms. Attempts at drafting these by the northern partner without consultation often result in confusion for the researchers and study participants. Collaboration of southern researchers and of translators for the local languages when needed is crucial for success in this step.⁽⁶⁾

Authorship and ownership of data

Examples exist in North–South research undertakings of behaviour that could be qualified as abusive, such as the publishing of data by northern researchers without acknowledging their southern counterparts, writing of publications in the North without sharing authorship with the South and exploitation of data analyses conducted by southern scientists without mentioning the originators.⁽⁷⁾ Drafting of cooperation agreements

with the participation of both parties should go a long way towards preventing improper conduct from either side. Such agreements should specify who owns the data, which should be by all researchers, and define the plan for disseminating the results at national and international levels by compiling a list of planned papers with their authors and giving the role of each, together with providing the guidelines for proposing new papers along the way by the group members.⁽⁸⁾ Involvement of the southern partners in the actual writing of the papers is part of the capacity-building process and as such should be considered essential.

Ethical reviews

It is generally accepted that research protocols need to be scrutinized by ethical review committees before the onset of a study to identify and deal with potential sources of harm to the research subjects. International research partnership projects require two ethical reviews, one in the sponsoring institution and the other one in the country hosting the study. If an ethics committee does not exist in the southern country, its creation, including training of the participants, should be undertaken and should constitute a preliminary project before the intended research starts.

The objections raised by the South against the need for a double ethical review are based on their perception of the universality of the ethical principles governing medical research. These principles were formulated initially by the Nuremberg Military Tribunal⁽⁹⁾ as a reaction to the atrocities committed against concentration camp detainees during the Second World War, who were subjected to harmful procedures against their will in the name of “medical research”. International agencies like the World Health Organization (WHO)⁽¹⁰⁾ and the World Medical Association⁽¹¹⁾ have developed and disseminated ethical principles for research. Since the ethics of medical research are universal, requiring a double ethical review is, in the view of its opponents, a masked attempt to impose northern ideology on the southern partners and a sign of lack of faith in the capacity of the South to carry out its own ethical monitoring. A number of studies evaluating the activity of the southern ethical committees listed by Ravinetto et al.⁽¹²⁾ revealed precisely their incapacity to eliminate all abuse against research subjects.

In reality, ethical review in the northern countries is required by not only the research institutions but also the sponsors, who need a guarantee that the research will be carried out in conformity with donor countries’ regulations. This review cannot be dispensed with. In a complementary way, ethical review in the southern country can do a better job of addressing such issues as the capacity of the local institution to conduct the research, the adequacy of informed consent, the involvement of the communities where the research will take place and the proposed reimbursement for the study subjects.⁽¹²⁾ Both the North and the South must work to ensure timely ethical review of the studies so that research designed to guide public policy and improve health gets completed as quickly as possible.

Capacity building in the South

The ultimate goal of the North–South cooperation is developing the research capacity of the South to the point where southern research institutions can efficiently compete for grants and deliver quality results that can guide national health policies. The framework for this process is partnership in conducting common research projects.

The capacity-development goal has two broad components: forming researchers on the one hand and strengthening infrastructure, as well as the managerial and administrative skills of the research personnel, on the other hand. Chandiwana⁽⁴⁾ describes the training of researchers at Blair Research Laboratory in Zimbabwe during 20 years of collaboration with the Danish Bilharziasis Laboratory. The training started with two-week research methodology courses during which interested and capable participants were identified. These were then enrolled for master’s and doctoral programmes in Europe. Training continued, as well as the retention of cadres, through postdoctoral fellowships. In parallel with these activities, reciprocal visiting scientist

arrangements contributed to maintenance of the close relationship between the institutions and to keep the scientific environment stimulating. Mentoring in research projects added to the capacity-building activities.

Funds were spent also on institution building and technology transfer. Aside from strengthening the managerial and administrative skills of the auxiliary personnel, the funds were used to supplement researchers' salaries, consequently contributing to the retention of highly qualified specialists.

A factor considered as negative in collaboration arrangements such as that between Zimbabwe and the Danish Bilharziasis Laboratory is that the training of scientists takes place mainly in the North. A strong, independent, world-standard and competitive research capacity needs to be developed in the South so that the South will be capable of training its scientists at home.⁽¹³⁾ At the same time we must acknowledge the importance of scientific exchange and exchange of scientists between research institutions, whether among southern institutions or between southern and northern institutions.

Addressing the brain drain

It is clear that many researchers participating in international collaborations, whether between northern and southern institutions or between northern and northern institutions, do not return home to work. One cause of the brain drain is the generous salaries offered to scientists in international organizations that are considerably higher than what they might earn in academia at home. The extent of this brain drain is by no means negligible. Evidence shows, however, that emigration is not an easy process and that many scientists, with the right environment in their home institutions, would prefer to stay near their families in their country of origin.⁽¹⁴⁾

Allowing for variations in individual ideals and expectations, the right environment for southern researchers in their home countries should consist of certain critical elements. The pay should be enough to support a decent and respectable lifestyle and educational opportunities for the researcher and family. Researcher incomes could be topped up, for instance by postdoctoral fellowships.⁽⁴⁾ The collaboration arrangement between a northern and southern institution should run over a long period, ideally more than a decade, to offer adequate time for pursuing the themes chosen by the scientists and to enable generation of substantive outcomes. Frequent visits to and contacts with other institutions, and participation in international forums would allow southern researchers to stay connected with the global scientific community, exchange ideas and initiate new projects. Career advancement opportunities should be available in the southern institutions.

Equitable and transparent use of funds

Developing research capability, both skills and infrastructure, requires funding to cover training costs, salaries, travel and housing for the scientists and other personnel to be trained abroad, as well as the infrastructure for equipping laboratories in the South. All traditional research grants from the North make provision for such training and infrastructure, consequently, there may be competition between the northern and southern partners over funding for research needs. Apart from this, the worldwide economic downturn has had its impact on research funding. An extract from a research interview done for a case study of North–South collaboration depicts the situation as seen from the North: “... we struggle to get funding more than they do now. I’d like to see them put us on a proposal that they write, because southern institutions are more likely to get funding”.⁽¹⁵⁾

Often the southern partner is excluded from exercising control over the structure or the use of the budget. Such problems could be avoided by involving the southern institution when the budget is being drawn so that the expenditure for both sides is realistically estimated and there is clarity on the destination of the funds. Both partner institutions should agree on the actual spending, and regular financial reports should be compiled by the donor representatives and made available to all parties involved.

3. Principles for successful North–South scientific collaboration

There are no entities regulating international scientific cooperation. However, the principles of successful partnership have been defined and redefined many times by writers and organizations.^(2,16,17) Summarized below are principles for successful North–South collaboration adopted from Stöckli et al.⁽⁷⁾ and that originate from the Swiss Agency for Development and Cooperation, a component of the Swiss Academy of Science:

- (a) Set the agenda together. Decide jointly on research questions, approaches and methods.
- (b) Interact with stakeholders. Who will use the findings? Governments? Other nongovernmental organizations? Collaborating with them from the onset will ensure the relevance of the research.
- (c) Clarify responsibilities. The work should be divided among the partners according to existing and future (acquired in the process) skills and capacities. Some responsibilities must be shared, such as disseminating the research and interacting with third parties, as well as ethical responsibilities.
- (d) Account to beneficiaries. The need to be accountable to funders is understood and accepted, but the need to be accountable to the future beneficiaries of the research is a more recent requirement, though not less important.
- (e) Promote mutual learning. Sharing knowledge and experience among partners enhances their ability to deliver results.
- (f) Enhance capacities. The transfer of knowledge, skills and technology is not unidirectional from North to South. There is a considerable potential in the partnership for scientists from the North to gain professional experience and to learn how to interact with different environments, cultures and people.
- (g) Share data and networks. “... both sides have information and relationships that are crucial for the success of their joint research project”.⁽⁷⁾ A system of incentives should be negotiated to encourage sharing. Both sides may be reticent about bringing this kind of sharing to the collaboration because data and networks hold power.
- (h) Disseminate results. The results should reach those who can exploit them to either improve people’s lives or generate new knowledge. The appropriate medium should be used.
- (i) Pool profits and merits. Authorship, the publications plan and patent rights should be agreed upon early in the planning.
- (j) Apply results. This requires that study findings be transformed into practical applications such as therapeutic protocols. Also, the beneficiaries of the applications should be sensitized to the new outcomes so that they can apply them in practice.
- (k) Secure outcomes. Once the common project is completed, it is important that the infrastructure and research skills of scientists and other personnel continue to be maintained in the South, either by continuing the North–South collaboration with new projects or by developing a South–South project.

4. Successful North–South research partnerships in Africa

A few successful, long-lasting collaborations have been described in the literature that resulted in the development of careers of a notable number of southern scientists who received training in both northern academic institutions and South Africa or Brazil, and also in considerable scientific output. From anglophone Africa, the cases in point include the collaboration of the Danish Bilharzia Laboratory with the Blair Research Laboratory and the Biomedical Research Training Institute in Zimbabwe for over 20 years in the last century,⁽⁴⁾ the equally long-standing collaboration between the London School of Tropical Medicine and the University of Witwatersrand School of Medicine in South Africa,⁽¹⁵⁾ and the partnership of the University of Zambia School of Medicine with the University College London Medical School.⁽⁵⁾ A number of publications from

francophone Africa are the product of the Groupe Franco-Africain d'Oncologie Pédiatrique (French-African Paediatric Oncology Group), which started in 2000 and currently operates 12 “pilot units” across the continent.⁽¹⁸⁾

Beyond translating into practice the principles of good North–South cooperation as summarized in Stöckli et al. (2012), what other factors contribute to the success of these collaborative enterprises? One special attribute of the project of the University of Zambia and University College London Medical School (UCLMS) is that it was an “African scientist-led, South–North partnership”.⁽⁵⁾ The southern institute established its own research themes in consultation with the country’s health authorities and applied for and managed the grants, with the UK partner playing a supporting role. From its beginning in 1994 to 2010, the project had received over 20 million euros in grants and produced over 100 papers. The findings of some of the studies have served to change WHO global policies on the management of tuberculosis (TB) and TB-HIV association. Other achievements were training of medical and auxiliary research staff, building up of expertise in clinical trials and developing infrastructure for infectious disease research. All this was possible because the southern partner had already established a track record as a credible partner prior to the collaboration with UCLMS, by having delivered on their part during another North–South research partnership with the University of Texas between 1991 and 1994.

Other significant elements can be gleaned from the collaboration between the London School of Hygiene and Tropical Medicine and the University of Witwatersrand.⁽¹⁵⁾ This partnership lasted for over two decades, and an important contributor to its success was the good personal relationships between members of the two institutions. A number of academics in the southern partner, who had completed their studies at the London institution, continued to maintain contacts there. An additional contributor to the good contacts was the seconding of an academic from the North to the southern institution for 10 years. Over the years, the partnership developed mechanisms for negotiating over the research priorities and funding issues to balance the objectives and interests of the participating institutions. Another important feature was the contribution of the northern partner to strengthen the PhD programmes in the South, to the extent that an equal number of participating scientists obtained their doctoral degrees in London and in Johannesburg.

5. The state of South–South research partnerships in Africa

The collaboration between research institutions from the South and the North originates in the need of developing countries to address their specific health problems while consolidating their own research capabilities. In their quest, they make use of both funds and research and training capacity offered by the North. Are there any benefits in two southern institutions cooperating, both of which in most cases have insufficient research capacity? To what extent is this South–South cooperation taking place on the African continent?

The answer to the first question is affirmative. Potential benefits from South–South partnerships have been highlighted by various scholars. Collectively producing a high-quality research output will contribute to creating a valuable track record and to increase the weight of southern institutions in their relationship with northern research centres and donors. Further, the South could in principle find more adequate solutions to its health issues from detailed knowledge of the local conditions. Also, the pooling of resources for research, besides providing the right size of workforce and infrastructure required for various projects, may generate better synergies and avoid duplication of systems or processes, which may result in better output at a lower cost. Finally, creating research opportunities of the right calibre in the South would contribute to minimize the brain drain that favours the North.⁽¹⁹⁾

Very little South–South collaboration is taking place in spite of the commitments expressed at the intergovernmental level, such as the Protocol on Science, Technology and Innovation adopted in 2007 by the South African Development Community (SADC). A quantitative analysis of the publications originating in the

SADC region from 2005 to 2008 in all areas of knowledge illustrates convincingly this point: only 3% of the publications were jointly authored by scientists from the countries in the region. There was, similarly, only symbolic cooperation between SADC researchers and their peers from non-SADC African countries, covering a mere 5% of the output. In comparison, almost half (47%) of the SADC papers were written together with scientists from the North. Out of the publications authored by African multinational teams, around 60% included northern scientists, indicating that much of the South–South collaboration was in fact driven by the North.⁽²⁰⁾

South Africa’s scientific output constituted 81% of all the SADC papers published during the study period. Such relatively strong research capacity makes South Africa an attractive partner for South–South scientific collaboration to build capacity in the neighbouring countries. Why then, in these post-apartheid years, has inter-African scientific cooperation not soared? The explanation has to do with the unavailability of funds: southern countries’ research budgets remain inadequate and donor money has often been insufficient for the type of partnership that results in building up of research capacity beyond the donor countries’ borders. A northern or southern donor needs to be involved who should be prepared to support such South–South partnerships. The strong research capacity in Brazil and India makes them potential strong research partners for African investigators, particularly for Lusophone Africa and East Africa, respectively. Alternatively, a northern research institution could be included in the consortium to constitute a “South–South–North” collaboration in which much of the training for research and supervision of common projects is handled by South Africa, Brazil or India with the guidance and assistance of the North as appropriate. There are obvious advantages in such an arrangement for both southern partners, including the relative proximity of the training country to the trainees’ home, which makes travelling and contact with the institution of origin easier, and possibly the lower risk of researchers “jumping ship” to join the host institution. Also, the training can be more closely matched to the type of pathology burden and infrastructure in the trainee’s country of origin.⁽²¹⁾

6. Conclusion

One factor associated with globalization is that diseases are no longer confined to a certain geographical area. This means that investing in research has universal benefit. Further, there is an obvious advantage in undertaking health research where disease abounds. This is the case with the resource-deprived countries, most of which have exceptionally high disease burdens. These diseases need to be controlled if these countries are to participate meaningfully in the world economy. This is the basis of the North–South research partnerships initiated in Africa. However, for the sake of equity and mutual benefit, such partnerships need to be structured along guidelines specifically created to avoid the multitude of problems encountered in past such collaborations. One such set of guidelines is provided by the Swiss Agency for Development and Cooperation.⁽¹⁷⁾ The future will see also more South–South partnerships for research capacity development in Africa, with the appropriate support of African governments and donors from the North and the South.

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Chapter 4

Responsible conduct of research

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Chapter outline

1. Introduction and background
2. Planning ethical research studies
3. Ethical clearance, institutional review boards and ethics committees
4. Conflict of interest
5. Responsible authorship
6. Scientific misconduct
7. Conclusion: a summary of recommendations

1. Introduction and background

Research is on the rise in Africa with the continent hosting over 40% of clinical trial study sites located outside the United States and other industrialized nations. In low- and middle-income countries, the number of externally sponsored clinical studies has doubled in recent years, which suggests that this increase is often not locally driven. There are many mostly unethical factors that have motivated the research shift to low- and middle-income countries, including their few regulatory standards, the opportunity for rapid accrual of participants and the cheaper cost of conducting studies and bringing drugs to market. There is need for the surge of research in the developing world to be accompanied by an understanding of the principles of responsible research conduct to ensure that advances in health care are equitably shared and achieved without exploitation.

Responsible conduct of research (RCR) can be defined as the practice of scientific investigation with integrity. It involves the awareness and application of established professional norms and ethical principles in the performance of all activities related to scientific research. The guidelines for ethical research practice include intellectual honesty, respect for human dignity, free and informed consent, privacy and confidentiality, justice and inclusiveness, and balancing risks by minimizing the harm and maximizing the benefits to research volunteers. When the rules of ethical research practice are not adhered to there is the risk of research misconduct. Research misconduct is defined as fabrication, falsification or plagiarism in proposing, performing or reviewing research or reporting research results.⁽¹⁾ In 2012, Fang et al.⁽²⁾ found that of the more than 2,000 study articles indexed by PubMed, 67.4% were retracted due to misconduct and almost half (43.3%) due to fraud or suspected fraud. Other types of misconduct included publication duplication (14.2%) and plagiarism (9.8%).

In Africa specifically, many clinical trials have been subjects of controversy or have failed due to ethical or moral deficiencies. Three examples are the studies on the prevention of mother-to-child transmission (PMTCT) of HIV sponsored by the National Institutes of Health (NIH) and Centers for Disease Control (CDC), the Trovan trial by Pfizer in Nigeria, and the Tenofovir trial in Nigeria, Cambodia and Cameroon. The PMTCT studies randomized HIV-positive women into two groups, one of which received a “more affordable” AZT but of an amount lower than the established efficacious dose⁽³⁾ and the other group received a placebo despite that there was proven effective treatment for the condition. This case demonstrates the double standards in research conduct, the controversies surrounding placebos, and the differing standards of care between

developing and developed countries. Ethical use of placebos can occur only for cases where there are no existing approved treatments for a condition, when there is disagreement about whether the standard treatment is better than the placebo (equipoise), if the additional risk posed by the use of the placebo is minor and withholding the existing standard therapy would not lead to serious or permanent harm, or if the study is anticipated to result in widespread benefits and the use of the placebo poses minimal risk to the individuals.

In the Nigerian Trovan trial, Pfizer administered Trovan to children during the 1996 outbreak of meningitis in Kano.⁽⁴⁾ This study committed several ethics violations: (a) Trovan had not been approved for treatment of meningitis, (b) informed consent was not obtained from study participants or their parents or guardians, (c) the principal investigator forged the institutional review board (IRB) approval to conduct the study because he could not obtain one since the hospital involved did not have an ethics committee, and (d) lower than recommended doses of Trovan were administered in order to cover the number of children in the trial. The consequences of this gross misconduct were severe: 200 of the children given the drug lost their hearing, sight or ability to walk. The records of 300 other children disappeared when the investigation into this misconduct began. Eventually Pfizer made a 75 million dollar settlement with the Nigerian government.

The Tenofovir trial in Nigeria, Cambodia and Cameroon, supported by Family Health International, had to be eventually stopped at all the sites due to controversy over quality control, poor compliance with laboratory requirements, the fact that most of the recruited sex workers were unaware of the risks involved in their participation and that no health care was provided if participants contracted HIV during the trial.⁽⁵⁾ Tenofovir is an antiretroviral prophylactic agent against HIV that is often used by sex workers.

While it is widely accepted that health research in African nations is necessary to promote health equity between industrialized and unindustrialized countries, the planning and execution of such research must be guided by the fundamental principles of human dignity and ethics.⁽⁶⁾ Though not enforced by law, adhering to international guidelines such as the Nuremberg Code, the Belmont Report and the Declaration of Helsinki^(7,8,9) must be required of any research to be accepted as credible by other scientists. These standards must also be observed if any study is to be published in respectable journals. In order to promote justice in research and the protection of vulnerable populations, special safeguards must be put in place to prevent coercion and selective exploitation of the poor.⁽¹⁰⁾ When planning research in low- and middle income countries, special attention must be paid to the motivations and goals of the research, establishment of ethics committees, promotion of responsible authorship, reporting of conflicts of interest, and discouragement of scientific misconduct by both the local researchers and external sponsors.

2. Planning ethical research studies

There are many ethical issues associated with the motivations and goals of clinical research in developing nations including those relating to placebo use, definition of standards of care and determination of benefits for the subjects vis-à-vis the larger population. When faced with such complex ethical issues, researchers should support studies that promote justice and do not exploit the local populations. The following conditions should be adhered to when planning a research study in a low- or middle-income country to ensure that it is ethical:

- (a) The study must be relevant to the health-care needs of the local population and country. For example, issues pertaining to the provision of the medications tested in the study beyond the study should be discussed before the study begins.
- (b) There must be a well-constituted institutional review board, an ethics review board (ERB), or an ethics review committee (ERC) at the local site in the country.
- (c) Research protocols must be reviewed and approved by the functional local ethics committee.

- (d) Participants should be exposed to minimal risk or harm, and need to be made aware of those risks before hand.
- (e) Research participants should be given adequate compensation for participation such as payment for missed work days.
- (f) Any conflicts of interest should be disclosed and the project should undergo an independent review to decrease potential bias.
- (g) Patient privacy, safety and right to withdraw must be respected at all times.
- (h) The overall research goals should be distributive, beneficent and non-maleficent.

In low- and middle-income countries, special attention must be paid to the study community. A staggering 90% of global health research expenditure is directed at diseases affecting only 10% of the world's population⁽¹¹⁾ This imbalance illustrates the importance of increasing research capacity in unindustrialized countries as well as directing research initiatives toward the conditions that afflict the local population. If the population of research participants and their government cannot afford the expensive therapies being tested by researchers from the industrialized countries, the study is considered unethical. While pharmaceutical companies need to be encouraged to include unindustrialized countries in multicentre trials, it should be regarded as unethical for the benefits of potential drug trials to be aimed at people outside the trial while the study participants are exposed to the risks of early-phase studies with no chance of sharing in future benefits. For instance, SmithKline performed a hepatitis A vaccine study on children in Thailand with the primary intention of developing a vaccine for foreign travellers. International rights documents such as the Declaration of Helsinki require an investigator to seriously assess the predicted individual risk burden and compare that risk with the foreseeable benefits first for the individual participants, then for the community involved in the research and finally for other communities at large.⁽⁹⁾ This is the ethical standard for comparing individual risks with societal benefits.

Prior to the start of any trial, the investigators also need to engage in discussion to decide on what will be owed to the participants and the community after the trial is completed. Ethical standards make it imperative that every volunteer should have access to the best-proven intervention that was part of the research at the end of the study.⁽⁹⁾ Researchers must determine how these benefits will be delivered, to what extent and to whom, for example if it will be the general community or just the participants. They must also consider at what cost and for what duration the intervention will be made available. These specific issues need to be discussed, agreed upon and documented in the research protocol.

3. Ethical clearance, institutional review boards and ethics committees

Up to 25% of clinical trials in developing countries are not subjected to proper ethical review.⁽¹²⁾ Institutional review boards or research ethics committees are responsible for reviewing protocols and ensuring that the risks and benefits to participants are balanced. These groups have the responsibility to ensure proper mechanisms are in place throughout the study to protect participants from coercion and other ethical lapses. Properly funded and fully functional review boards have also been found to increase productive research undertakings in resource-poor regions.⁽¹³⁾

A World Health Organization (WHO) survey of African Member States in 2003 noted that of the 28 countries that responded, 36% did not have a national ethics committee, but a majority of sites had other mechanisms to review submitted study proposals.⁽¹⁴⁾ In 1999, the WHO tropical disease research group conducted two seminars analysing the status of ethical review in Africa, Asia and the Western Pacific and identified several weaknesses.⁽¹⁵⁾

- (a) procedures for reviewing protocols and informed consent forms did not exist;

- (b) trained institutional review board members were lacking;
- (c) resources and funding were insufficient;
- (d) monitoring systems did not exist for ongoing research;
- (e) meetings of institutional review boards lacked quorum;
- (f) the reviewing bodies lacked independence.

These weaknesses have contributed to laxity in enforcement of ethical standards and poor regulatory oversight. Furthermore, some of the governments in the developing countries believe that ethical review of research proposals by ethics committees is unnecessary,⁽¹⁶⁾ and often a single government official, rather than a committee, grants research approvals. This creates a situation with high potential for bias and corruption.

Developing countries should be assisted in establishing reliable and operational bioethics review systems at the national, regional, district and institutional levels. Research ethics committee membership should be diverse and should include physicians, scientists and other professionals such as nurses, lawyers, ethicists and the clergy. A WHO study⁽¹⁷⁾ observed that membership of many institutional review boards or research ethics committees was disproportionately made up of physicians and government officials, which is unrepresentative of the general population. It is important that qualified lay people of different ages and gender also be included to represent the cultural and moral values of the local community.⁽¹⁸⁾

Externally sponsored trials have the additional requirement of dual review of the research protocols, by the sponsoring country and at the local site where the study will be conducted. However, the primary and final judgment will be made by the review board at the study site. This can be beneficial, as the expertise of the sponsoring institutional review board is combined with the familiarity of the local review board with the site to reconcile the regulatory requirements with sociocultural circumstances.

Improvement is needed in training of institutional review board members in research ethics. In a study involving 12 sub-Saharan countries, 38% of review boards stated they had received no training in research ethics, and 92% of respondents reported being inadequately trained to properly review and monitor clinical trials.⁽¹⁷⁾ The most common training gaps identified were in the knowledge of scientific study designs, risk assessment, phases of clinical trials, monitoring approved clinical trials and handling post-trial access to benefits. Opportunities are increasing in low-resource situations, especially in Africa, for training institutional review board members to help fill these knowledge gaps. These opportunities vary from web-based courses to extended fellowships.⁽¹⁷⁾ There is also urgent need to advocate for inclusion of courses on research and medical ethics in undergraduate medical education for all health-care professionals in unindustrialized countries, where patients are more vulnerable to exploitation and are less aware of their legal rights.⁽¹⁹⁾

Ethical review of research protocols and the subsequent monitoring of the study require adequate staff and resources as well as extensive ethics training for the review team members. Review committees should be independent and composed of individuals trained in science, statistics, ethics, and law, as well as representatives from the community to give voice to the social values, priorities and concerns of potential participants.

4. Conflict of interest

Even with an institutional review board or ethics committee in place, researchers must be conscious of potential ethics violations over the entire course of a research study. A conflict of interest exists when researchers or their institutions, families, reviewers or editors have financial or personal relationships that may inappropriately influence the researcher's professional conduct. Conflicts of interest can also include motivations to achieve personal prestige or acquisition of stock in a firm connected with the study.⁽²⁰⁾

Financial impropriety is the most common type of conflict of interest and often arises from the interaction of physicians with pharmaceutical companies or other research sponsors. If undeclared or unmanaged, interactions with external firms can impact clinical decision-making by physicians. For instance, researchers receiving remuneration from pharmaceutical companies are more likely to be biased in supporting the safety and efficacy of drugs manufactured by those companies.^(21,22) Therefore, clinical investigators have the responsibility to ensure that research agreements do not interfere with independent access to and analysis of data or the freedom to prepare and publish manuscripts of the findings.⁽²³⁾ Members of review boards must also declare any conflict of interest and should keep this information updated throughout their review board participation. Conflicts of interest are not confined to individual investigators or review board members but can also occur at the institutional level, for example associated with ownership of a patent that may bring in a financial windfall if the study is successful.

Conflicts of interest are common and are not considered unethical if they are declared openly. Unfortunately, undeclared conflicts of interest are common ethics violations. A meta-analysis of conflict of interest in 1998 showed that of the 69 authors observed, 63% acknowledged a financial conflict of interest yet only 3% had declared this.⁽²¹⁾ Additionally, only 29% of cancer studies published in high-impact journals disclosed conflict of interest.⁽²⁴⁾ To properly manage conflicts in a study, the investigators and committee members must first declare potential sources of conflict before being allowed to participate in the review of the research protocol or serve on the review board that will grant approval to the proposed research. To address a possible conflict, an individual must first be aware of the potential ethics violations and consider consequences of non-disclosure. A review by the institutional review board of a protocol with declared conflict of interest should require a plan to manage the conflict. Oftentimes review boards require changes to be made in the research protocol to minimize the conflict of interest. But they might require that the influence or duties of the investigator associated with the conflicting segment of the project be limited; that the article that is the source of the conflict of interest be relinquished for instance stocks be disposed of; or that the investigator resign. If these options are not feasible, the investigator may be denied participation or may be replaced with one without such an encumbrance. Institutions such as academic centres and hospitals need to provide formal institutional guidelines and maintain a conflict of interest committee to enforce them. They should also have annual training for all faculty, research staff and students to guarantee awareness of and adherence to such policies.

Unmanaged conflicts undermine patient and public trust as well as the scientific integrity of a study. Clinical investigators should minimize conflicts by demonstrating commitment to their primary responsibilities and should avoid or minimize consultations for and major stockholding in pharmaceutical and biotechnological companies and their agents. To avoid conflict and ensure transparency, stocks that could be a potential source of conflict of interest can be placed in a blind trust, and consultant or advisory positions must be declared to all parties involved. Researchers should ensure that their external activities or financial interests do not interfere with their primary commitment to patient well-being and to ethical research for the purpose of advancing medical knowledge.

5. Responsible authorship

A survey on misconduct among some Nigerian researchers found authorship disputes to be a major ethics problem.⁽²⁵⁾ Authorship is highly valued in academia, and motivation for prestige can sometimes lead to unethical behaviour. An author is considered to be someone who has made substantive intellectual contribution to a published study.⁽²⁶⁾ Research authors should be able to identify who in their team is responsible for each aspect of the manuscript and to be confident in their own ability and integrity. There are three specific criteria that must be met in order to receive authorship credit.⁽²³⁾

- (a) making substantial contribution to study conception and design, as well as acquisition, analysis and interpretation of data;

- (b) drafting the research article or revising it for important intellectual content;
- (c) approving the final version of the research paper to be published.

Researchers and authors should be aware that acquisition of funding, collection of data and general support of research groups alone do not constitute authorship. Many research misconduct scandals arise from honorary or “gift authorship”, often awarded in exchange for authorship on another paper or as homage to a head of a department. There are many examples in which senior or supervising authors with no knowledge of the details of a study had to suffer serious consequences for accepting authorship of the research paper.⁽²⁷⁾ Individuals who do not fit the author’s criteria can be recognized in the acknowledgements section or as contributors. This includes individuals who provided purely technical or writing assistance or served as the department chair. Groups of individuals who have contributed in these ways may also be listed under headings such as “clinical investigators” or “participating investigators” with their functions or contributions described in some detail.⁽²³⁾ Financial and material support also must be acknowledged.

Multicentre trials requiring collaboration often have difficulties assigning authorship. To avoid such problems, the research group should discuss and resolve questions of authorship, including the order of authors, before commencing and during the course of the study.⁽²⁸⁾ There are many methods of determining authorship, including the use of a score-based system in which the authors’ order is based on individual contributions. Another method is adhering to prearranged roles, guidelines or agreements made early in the study between the principal investigator and collaborators.

When authors have been identified, both individual and group authors have the responsibility to ensure data integrity and accurate data analysis. All authors are accountable for ensuring that their research is in accordance with international guidelines in order for the findings to be published. Failure to reject negative or inconclusive results counts as scientific misconduct.

6. Scientific misconduct

A British Consensus Panel in 1999 defined scientific misconduct as “behaviour by a researcher, intentional or not, which falls short of good ethical and scientific standards”.⁽²⁹⁾ Scientific misconduct hampers the progress of medical knowledge and increases the risk burden for study participants. Forms of scientific misconduct or dishonesty include fabrication or falsification of data, plagiarism, gift or ghost authorship, and failure to declare conflict of interest or commitment to a party with interest in the research outcomes.^(1,30) These are serious offences that create mistrust for the profession, undermine research integrity and stall scientific progress. Clinical researchers must remember that the management of millions of patients is influenced by the scientific validity and accuracy of information obtained from clinical trials.

Unfortunately, it appears that scientific misconduct is quite common in developing countries. A survey of researchers in Nigeria showed that 68.9% of them admitted to at least one form of scientific misconduct, 42% of whom had falsified data or had been involved in plagiarism. These researchers attributed their misconduct to perceived inadequacies in institutional rules and guidelines.⁽²⁵⁾ This emphasizes the importance of establishing codes of good scientific practice and creating review boards to investigate allegations that arise in research institutions.

Reporting suspected research misconduct is an important responsibility for all members of the academic community. This process can be promoted if institutions enhance protection of “whistleblowers”. Additionally, researchers, institutions or sponsors accused of misconduct or violation of ethical guidelines should be investigated by the research ethical committee and reported to the appropriate national agency, the sponsoring institutions and funders. Consequences of proven research misconduct range from legal action, especially in cases of fabrication and plagiarism, to restitution, for example being required to issue a public apology or to return the money that had been received.⁽³¹⁾ Other penalties may be disqualification

from serving on advisory or peer review committees, ban from conducting research, and termination of employment.

7. Conclusion: summary of recommendations

In its most basic form, the ethical conduct of research is rooted in the requirements of societal value of the research to the host community, scientific validity, fair subject selection with favourable risk–benefit ratio, and a thorough independent review. When determining how to interpret various ethical guidelines, health researchers must realize that international research is directed towards advancing collective medical knowledge and should protect populations in industrialized and unindustrialized countries equally.

Many options exist that can be instituted to improve the ethical conduct of research in Africa and other low-income regions. First, health researchers must take responsibility for ensuring the protection of the rights of trial participants. They must also commit to adherence to the research protocol, personally conducting the research, informing patients that the drugs are being used for experimental purposes, ensuring informed consent, reporting adverse events, and reporting any changes to the study protocol or any unexpected problems.^(9,32) These rules can be adapted by government agencies in resource-poor regions to ensure accountability and a sense of moral responsibility. A course in research ethics should also be added to undergraduate course work for students of medical and allied disciplines to foster nurturing of more “ethically aware” future medical research professionals.

Since estimates categorize over 80% of ethical review committees or boards in low- and middle-income countries as being below standard, creation of local institutional review boards should be a major priority for these countries. But such a local review committee may still need support from external sponsoring institutional review boards, especially in handling controversial issues and membership selection and training. Until the ethic committee is developed and is fully functional at the local site, regular communication between the sponsoring and local institutional review boards will provide the much-needed education and will assist the local institutional board to build research ethics capacity. This will also provide an avenue for outside sponsors to learn about the laws and regulations of the country where the study will be conducted. Efficient review boards require members who have received training on ethical principles and are involved in continued education to update their knowledge.⁽³³⁾ Online courses have been suggested as an accessible and proven means of educating local researchers⁽³⁴⁾ and would also be beneficial for international sponsors. A pilot project in Nigeria is assessing the use of long-distance education to develop national ethics guidelines.⁽³⁴⁾ That model, which uses an online module for ethics education based on the National Code for Health Research Ethics, has been developed and validated on the CITI web site. This long-distance and accessible training method can be adopted by other countries that seek to expand their research activities.

Respect, dignity and welfare for research participants must start from both political and scientific African authorities. They must recognize the need for the ethical conduct of research as a necessity for improvement of health care. In accordance with this, each country should have a set of rules and regulations to guide human research based on internationally recognized guidelines that can be adapted to fit cultural and traditional norms. In addition to advising on the sociocultural applications of international research rights, community representatives should be involved in the various stages of research planning and implementation. Such involvement will promote a sense of ownership in the local community by sensitizing them to the need for the research and better understanding of the research, and improve participation in the research and acceptance of its outcomes. This would ensure effective dissemination of health information, creation of adequate informed consent documents in simple language understood by the community, and effective subject recruitment, retention and follow-up. Community representatives should be individuals from the study population who understand the local laws and cultural values, such as religious requirements and gender roles.⁽³⁵⁾ Local researchers must take seriously the responsibility of safeguarding their communities and start demanding high ethical standards. To accomplish this, they need to be trained in

ethics and human rights as they relate to health and research, and in local languages. Ethical conduct of research should be should be regarded as a value for the societal structure as a whole.

Globalization of research should aim to minimize the disparity seen between the health of developed and developing nations. Research participants in Africa and other resource-poor regions are often more vulnerable to exploitation due to a combination of poverty, illiteracy and inaccessible health care. To avoid exploitation, trials conducted in such a region must be geared toward the local health needs of the people in that region. Some basic ways to ensure this is to minimize inducements, which pressure prospective participants into actions that may be harmful to them. Acceptable compensation for lost time or wages and cost of transportation are usually appropriate but must first be approved by the local ethics committee.⁽³⁶⁾ Also, informed consent, ideally written at the sixth-grade level, should be obtained from each participant, and the research protocol should be explained in detail to participants, including the description of the risks.⁽³⁷⁾ It should also be made clear to participants if no immediate benefit of the research is expected. These efforts, along with other safeguards that have been discussed in this chapter, will improve participant understanding of research, encourage collaboration with, rather than exploitation of, developing nations, and ensure that low- and middle-income countries increase their research capacity and promote the health of their own populations.

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Chapter 5

The grants process

Damali Martin and Makeda Williams

Chapter outline

1. Introduction
 2. Communicating with your programme officer
 3. Writing the grant
 4. Understanding how agencies select grants for awards
 5. Grants management
 6. Summary
- Appendix: NIH grants process for international scientists

1. Introduction

Advances in battling cancer are principally attributed to the systematic process of identifying questions to understand the basic biology of the disease; applying this understanding to clinical and population studies; gathering, cataloguing and analysing data in various populations and clinical settings; and continuing to train new investigators to help accelerate these efforts. This process is dependent upon generation of innovative, practical and feasible ideas based upon existing knowledge but with the promise of expanding the knowledge to decrease mortality and morbidity from cancer or other diseases. This entire enterprise of cancer research has required a significant infusion of public and private funding. The process by which such funding is distributed is competitive, which has allowed for the most meritorious science to be supported.

Research grants are the main vehicle by which research funding is awarded to support scientific ideas proposed by investigators. In general, most institutions offer two main avenues to obtain support for research, either intramural or extramural funding. Intramural funds are money provided directly by the institution to its staff to carry out research. Such funding often supports the salaries of the research personnel and provide the required resources such as equipment, space, infrastructure and basic laboratory supplies. Intramural funding may or may not require writing of specific proposals for new ideas and constitutes the base funding for research. In most institutions in Africa, intramural research funding is both limited and may be the only funding that has historically provided research support.

Extramural funding, money from outside an institution or funding agency, always requires writing of a specific proposal. Such funding is extremely competitive and requires meeting very stringent criteria, as well as institutional support and research infrastructure, including administrative support for the scientists. Extramural funding may require a successful history of funding. Most research funding requires a demonstration of the feasibility of the approach, some preliminary data and confidence in the ability of the investigator. Therefore, it is best to begin by either using intramural funding to develop preliminary data or to approach agencies that will provide seed funding for pilot projects. In Africa, such funding might be provided by the African Organization for Research and Training in Cancer through their programme Beginning Investigator Grant for Catalytic Research (BIG CAT).

Generally, extramural funding is often subcategorized in two: investigator-initiated and agency-solicited funding. Investigator-initiated funding supports a wide spectrum of research based entirely upon the scientific ideas proposed by the investigator. Agency-solicited funding supports research for broad or defined areas for which an agency has specifically requested proposals. Irrespective of the type of research proposal, it is important to understand the detailed processes, administrative requirements, timelines and application procedures to successfully apply for funding. Many funding agencies usually have personnel or programme officers who will be the primary source of information on the scientific, funding and programmatic matters and will help guide investigators through the grants process.

2. Communicating with the programme officer

Investigators are often told to “contact your programme officer” before embarking on their grant writing adventure, yet very few principal investigators do so. Investigators provide many reasons for this, ranging from “they (the programme officers) would probably reject my proposal” to “I don’t know what to say” (1). The thought of speaking to a programme officer can be intimidating for scientists, especially those just starting their careers. However, communicating and maintaining a professional relationship with the programme officer has become integral to grant writing success. A programme officer could help the researcher determine whether the proposal is a good fit for the programme, guide the researcher towards an appropriate funding track or provide useful information on trends in research (1). Some guidelines to help you communicate effectively with your programme officer are provided below.

Before contacting your programme officer:

- (a) Look for the programme officer’s area of expertise to ensure that it is in line with your research ideas. This will minimize the amount of detail that will be needed to describe your proposal and will also ensure that you are receiving the advice that will help propel your research forward.
- (b) Write a brief summary describing your research project. This description should include some background information that logically leads to the hypothesis, the specific aims of the study, the desired outcome and any future studies that could follow. The investigator should also give a brief explanation as to how this research fits into the funding agency’s mission and how it would move the area of science forward over the next three to five years.
- (c) Do not exceed two pages in your description. Try to get to the heart of the matter within the first page. If you have difficulty expressing your ideas in two pages you need to rethink your proposal.

When contacting your programme officer:

- (a) Always use email first. In the email, you should clearly state the questions and comments that you would like to address, the kind of feedback you would like and your available time to speak or meet over the next few weeks. It will also be useful to send the brief description of your project that you prepared. Give the programme officer approximately one week to respond, as he or she probably receives several emails of this nature a day and will need time to read and respond appropriately to each request.
- (b) When you receive a response read it carefully. If the programme officer recommends someone else to contact, follow up with the recommendation. Ask the programme officer if it is alright to use his or her name in your email to the next programme officer. If the programme officer wants more information from you he or she will usually make the time for a scheduled phone call.
- (c) Do not “cold call” your programme officer. Programme officers are usually extremely busy and often work around tight deadlines. In addition, they will need time to prepare for your call. If you do cold call your programme officer, he or she may not be able to devote the time that your research idea deserves and that will potentially hurt your proposal in the long run. If you must call, use this opportunity to make

an appointment for the appropriate amount of time that will be needed for a constructive discussion of your project.

When talking to your programme officer:

- (a) Discuss the proposed research project in the context of the agency's interest and try to indicate how the project will address the funding agency's objectives or mission.
- (b) Discuss how the proposed research project will advance the field.
- (c) Do not promote your project by criticizing the research already in the field because you might be criticizing the research that is supported by the programme officer. Just stick to the selling points of your proposal.

After talking to your programme officer: follow up with a thank you email.

If you are nervous about communicating with your programme officer, ask a senior investigator or mentor for advice or ask to sit in on a conversation between that senior investigator and his or her programme officer. Also, role play with someone who has experience in speaking with a programme officer until you feel comfortable pursuing this on your own.

3. Writing the grant

General advice for preparing a grant proposal

A grant proposal is first and foremost a planning document in which you provide the granting agency information on the background of the specific problem (hypothesis) you want to address along with supporting details from an unbiased literature analysis. In addition, you will provide suggestions for tackling the problem and some background data that you have independently generated to support your hypothesis. This planning document should also show the feasibility of your approach and demonstrate the skills and the expertise that will be required to successfully address the problem. It is also important to realize that the proposal is often one of many reviewed by other experts in your area who themselves are both engaged in similar research or are quite familiar with the current advances in the field. Your success is therefore very dependent upon the quality and attention to specific details in the proposal.

The most important element in the preliminary phase of your work for successful grant application is your ideas. These ideas should develop a unique and innovative research question that will have impact in your field. This requires "doing research on the research" to investigate whether the research question if answered successfully could address a gap in the field and have significant impact on clinical practice, public health or scientific knowledge. This involves monitoring and surveying the literature in your area of interest and developing a network of positively critical colleagues with whom you can openly discuss these ideas and fine tune them to make them both stronger and clearer. Undertaking a literature search will also help you to find support for your ideas and to prepare a strong background illustrating the significance of the problem that is being addressed. It is advisable that you do not rehash research questions that have already been published as this is unlikely to be supported, unless you can demonstrate why the data need to be re-examined.

Once you are confident in your research question and overall goals, your next step will involve conceptualizing the key elements of the research plan, which are the specific aims and hypotheses, background and significance, literature review and preliminary data, research design and methodology, budget, timeline, and ethical considerations. Some investigators start with a planning document that serves as a blueprint of the specific steps that they will take to reach the goals of the proposed work and identifies the team of players that will be needed to help achieve that goal. Planning should include assessment of

resources from your institution, potential collaborators and mentors, as well as other resources that are tangible and necessary. Next, you should put together a strong research team of scientists and administrators who are subject-matter experts in the field. The research team will conduct research with you, so you need their input and constructive critiques for the research plan before submission. In addition, you should ask experienced researchers or mentors for advice on the research plan. Contacting the programme officer during this phase is also advisable. Finally, you should review the application rules and requirements, such as those pertaining to the application format, budget, biosketches, appendices, etc., along with the research priorities of the funding institution so that you can plan ahead effectively before submitting your proposal. Box 1 provides a list of questions that will act as a guide during the initial planning phase of your proposal.

Box 1: Planning document questions

What is the current status of the science?

What are the research gaps that exist? What does the literature say about these gaps?

Has this been done before, and if so, was it effective? Why or why not?

What are the significant needs that I am trying to meet and what is the potential impact if I meet those needs?

Will the impact be felt at the local, state or national level?

Is the proposal likely to produce a new concept or confirm an existing concept?

Will the proposed research lead to other significant studies? What are some of the potential future steps if I am successful?

What funding agencies are interested in this problem? Does solving this problem fall under their mission or areas of interest?

What are my research questions or objectives? What are the hypotheses that will help to address the research questions or objectives? Do I have evidence supporting my hypothesis?

Are the aims logical and do they help to address the hypotheses?

Am I qualified to carry out this project? What expertise do I need and how can I get it? Do I have collaborators that will fill the expertise gaps and are they qualified and competent?

How will I do the study? What are the best procedures and are they adequate or feasible for the research?

Key elements of a research plan

To be competitive for research funding, every research plan should include the following key elements in the application:⁽²⁾

Abstract

Usually 200 to 300 words, the abstract provides a brief synopsis of the investigator's research question, objectives, significance and research methodology. This is your opportunity to make a good first impression especially to those reviewers who may not read your entire grant proposal. In addition, some agencies like the National Institutes of Health will use the abstract to help assign the project to the appropriate study section and programme officer. Therefore, it is important that the abstract be clear and capable of standing on its own and apart from the proposal. Make sure to include key words and phrases and do not use abbreviations.

Specific aims

The specific aims are the research plan's focus and objectives. In other words, the specific aims state clearly what will be done in order to answer the proposed research question. They should be focused and measurable. In addition, they should be accomplishable within the time specified in your proposal. Generally, it is a good idea to limit your specific aims to a maximum of four, as too many aims may come across as overambitious. Specific aims may be accompanied with a brief introduction or abstract about the nature and importance of the research problem and the hypothesis that will be tested. Make sure that your hypothesis, as well as the accompanying study aim, is clear. Do not bury it in the text of the grant.

It may be easier to split the specific aims section of your application into two parts. The first part or the body of the section should open with three to four creative thoughts that will really grab the reviewers' attention. In particular, you will want to state what is known about the research area of interest, what is unknown about it and why this lack of knowledge is important and should be pursued. In addition, you can state the overall goal of your scientific plan and the specific goal of the proposal. You can also use this section to briefly describe any resources you have that would help you achieve the goal of your proposal. Box 2 presents an example of the body of a specific aim.

The second part of your specific aims section will list each aim and the hypothesis that it will test. Some investigators may choose to include the null hypothesis also, but this may not be necessary. Be sure to arrange the specific aims in the order of the research process. The specific aims will probably be related to each other, but it is important that they are not dependent on each other; that is, your ability to work on the second and third specific aims should not depend on your ability to successfully finish work on the first aim. This mistake is usually a major pitfall and can dampen enthusiasm for research. When writing your specific aims, use action phrases such as "to develop", "to compare" and "to investigate". Specific aims could also be accompanied by sub-aims, but you should exhibit caution with that. If you find that you have more than two sub-aims for a specific aim, then your specific aim may not be as focused as it should be and you probably should rethink it. Refer to Box 3 for a guide to help you in developing your specific aims.

Box 2. Writing specific aims: body of a specific aim (provided by Rebbeck, TR)

Inherited mutations in the *BRCA1* and *BRCA2* (*BRCA1/2*) genes are associated with an increased risk of developing breast and ovarian cancer. It has also been well documented that hormone-related exposures alter the risk of breast cancer. Use of bilateral prophylactic oophorectomy (BPO) significantly reduces both breast and ovarian cancer risk in *BRCA1/2* mutation carriers (Rebbeck 1999, Rebbeck 2002, Kauff 2002). The reduction in breast cancer risk after BPO is likely to be due ovarian hormone ablation. Other hormonal exposures including oral contraceptive use, hormone replacement therapy (HRT) use, and reproductive history also appear to influence breast cancer risk in women from the general population and those who carry *BRCA1/2* mutations. Finally, genes involved in steroid hormone metabolism, including the androgen receptor, *AIB1*, and the progesterone receptor may modify breast cancer risk in *BRCA1/2* mutation carriers (Rebbeck 1999, 2000, Runnebaum 2001, Narod 2002).

These observations argue that hormonal exposures, including the use of BPO and post-BPO HRT use, may modify breast cancer risk in *BRCA1/2* mutation carriers. BPO is now widely recommended for women who carry *BRCA1/2* mutations after the completion of childbearing. Due to quality of life issues (such as hot flashes and disordered sleep) and risk of osteoporosis associated with premature menopause, HRT is often used following BPO. However, only limited data are available regarding the timing of this surgery relative to reproductive events, or the type and timing of subsequent HRT use. More information is urgently needed to help guide these clinical decisions.

The goal of this proposal is to understand the relationship between clinically relevant hormone exposures (including BPO, HRT use, and reproductive history) and breast cancer risk in *BRCA1/2* mutation carriers. We will evaluate the relationship of BPO, HRT, and other factors on subsequent breast cancer risk, and will evaluate breast tumor markers that may elucidate biological pathways of breast carcinogenesis in response to hormone exposures. The data generated by this proposal will aid clinical decisions about the type, timing, and duration of post-BPO HRT use, and will provide insight into tumor biomarkers that elucidate the biological basis for *BRCA1/2*-associated breast cancer risk assessment, prevention, and treatment.

In our previously funded grant (R01-CA83855), we developed the resources of the multi-center PROSE (“Prevention and Observation of Surgical Endpoints”) consortium that has collected data on almost 2,000 prospectively identified *BRCA1/2* mutation carriers. Thus, we have extensive capability for ongoing prospective recruitment and the evaluation of clinical and biological factors associated with *BRCA1/2*-associated cancer risk and risk reduction. These resources and our preliminary data motivate the following specific aims in this competing continuation grant proposal:

Opening Statements and what is known

What is not known and why is the knowledge important

Overall long-term goal and overall objective for proposal

Do you have the resources and ability to do the research?

Box 3: Writing specific aims section: specific aims with hypothesis (provided by Rebbeck, TR)

Specific Aim 1: Evaluate the effect of post-BPO HRT use on breast cancer risk reduction.

Null Hypothesis 1.1: Short-term use of post-BPO HRT does not change the magnitude of breast cancer risk reduction conferred by BPO.

Null Hypothesis 1.2: Type of post-BPO HRT use (e.g., combined estrogen/progesterone therapy vs. unopposed estrogen use) does not affect the magnitude of breast cancer risk reduction conferred by BPO.

Specific Aim 2: Evaluate whether the timing of BPO with respect to age and reproductive events affects the magnitude of cancer risk reduction.

Null Hypothesis 2.1: The magnitude of breast cancer risk reduction is independent of timing of BPO.

Null Hypothesis 2.2: The magnitude of ovarian cancer risk reduction is independent of timing of BPO.

Specific Aim 3: Evaluate the effect of HRT and BPO on histopathological and biomarker-based characteristics in breast tumors, considering tumors arising from inherited BRCA1 and BRCA2 mutations separately.

Null Hypothesis 3.1: Breast tumor characteristics do not differ among women diagnosed with breast cancer after BPO compared with women who have not undergone BPO.

Null Hypothesis 3.2: The use of post-BPO HRT does not influence breast tumor characteristics.

Therefore, Aims 1 and 2 address important clinical issues in the management of BRCA1/2-associated cancer risk, and Aim 3 will establish a biological rationale for the improved understanding of breast cancer risk and prevention in BRCA1/2 mutation carriers. We hypothesize that BPO, HRT use, and reproductive history may influence both the clinical and biological manifestations of cancer risk in women who have inherited a mutation in BRCA1 or BRCA2.

Specific Aim
1 with
hypothesis to
be tested

Specific Aim
2 with
hypothesis to
be tested

Specific Aim
3 with
hypothesis to
be tested

Closing
statement
with public
health
impact

Background and significance

This section will include parts of the literature search that was performed during the creation of your planning document. In this section, you will present a review or history and key findings or current knowledge in the research area of interest. You will also state the scientific gaps that exist, which should then naturally flow into how your proposal will address the gaps. Make sure to state the significance of the proposed research and how, once it is completed, it will impact the scientific area, clinical practice or public health. This is not an opportunity to write a research dissertation; therefore, provide only the salient points that will help sell your proposal, as the reviewers will most likely be familiar with the research area anyway. In addition, make sure that the literature referenced is the most recent. If you have access to the list of scientific reviewers for your research, it certainly will be a plus to include their publications in your background section.

Preliminary data

Not all funding agencies or funding announcements will require the principal investigator to present preliminary data. However, if preliminary data are required, it is very important that they actually support the hypothesis or research question. Therefore, you should pay particular attention to your selection of data. Do not present preliminary data just for the sake of doing so, as this will diminish the impact of your proposal and will probably leave the reviewers perplexed and confused. Also, present data that will show that you are capable of carrying out the research aims and that will give useful information about your project.

Research design and methodology or approach

This is probably the most challenging section to write. The purpose is to show in detail how the research will be performed. A poorly written research methodology section will cast doubt on your ability to do the type of critical thinking that will lead to successful completion of the research. The section should clearly describe:

- (a) The study design. For example, is the study a cohort, case-control or case-only study? Explain why this design is the best to achieve your results and include a timeline for the steps of the proposed research.
- (b) The study sample or subject recruitment. Describe the samples that you will use to do the study. For example, will you use blood, DNA or tumour tissue? How will the samples be processed? Will you need to collect the samples or are these samples from a previous or ongoing study? If you are recruiting patients for your study you will need to describe the study population and list your criteria for including or excluding them.
- (c) Data collection tools. Describe the instruments to be used to collect the data, such as questionnaires administered during subject recruitment. It may be necessary to indicate that the collection method is acceptable in the field by citing other references. If the data collection method is novel or unique, describe how it is better than the “gold standard” for your study area.

Data analysis and expected outcomes. Describe how the data will be analysed. For example, will you use logistical regression? Do you have enough power or is your sample size big enough to address the research question? Is your data analysis plan clear and easy to follow? Are you using a novel data analysis method, and if so, why is it a better method? Make sure that your data analysis plan is clear and easy to follow. Also state the expected results of the study and what their impact will be on public health.

Potential pitfalls and limitations. Many investigators are hesitant to describe potential pitfalls and limitations of their research for fear that the reviewers will hone in on these. This is not true, as all scientists know, no research is perfect! Failure to state the limitations will probably lead the reviewers to think that the investigator was not thorough in developing the proposal. Take time to describe all the potential pitfalls and present alternative methods or solutions to overcome these. In addition, clearly state what your study will answer and what it will not be able to address.

Budget

Budgets should include direct costs such as expenses for personnel, consultants and support staff, equipment, supplies, travel, patient care and infrastructure alterations and renovations, and indirect expenses such as service costs, computer-related expenses, incentives for research subjects and facility rental. The principal investigator should make sure that the budget is reasonable and realistic to achieve the research project goals. Review panels will not score favourably for budgets that overestimate or underestimate research project costs.

Additional elements of a research grant application

Several other items are typically required to complete a research grant application.⁽²⁾

- (a) **Cover letter:** Including a cover letter with the application is a great way to provide the title and brief description of the research aims and to identify the announcement calling for submission of the grant application.
- (b) **Title:** The title is important and should be concise and convey what the project is about.
- (c) **Key personnel:** This section demonstrates that you have assembled the right team to conduct the proposed research. It is important to highlight the expertise of all the key personnel and clearly define their roles and their level of effort and time commitment for the project. In addition, you may want to use this section to describe your experience in managing previous projects, as this will show the reviewers and the funding agency that you are the right one for the job.
- (d) **Biosketches:** Biosketches allow the investigator and the research team to show the review panel their knowledge, skills and experience. Biosketches should be brief and include your name and position title, education and training history, a personal statement on your experience and qualifications for the research project role, previous positions and awards, selected peer-reviewed publications, and either completed or ongoing research support work.
- (e) **Resources and environment:** You will need to describe your research environment. Do you have access to the resources that you need? Does your institution have the equipment needed to do the research? Do you have other colleagues who will support your growth as an investigator and, more importantly, are the leaders in your institution supportive of your proposed research?
- (f) **Letters of support:** Letters of support will show the reviewers that you have access to needed samples, expertise or institutional resources. They can also be used to outline the nature of collaborative relationships or give proof of previous collaborations with personnel who will help you in your proposed research.

Ethical considerations: Indicate whether the research subjects are human or animal. If human subjects are requested, you should ensure protection for their participation with approval for your research from the institutional review board. If animal subjects are requested, you should provide justification for their use and care, and receive approval from your institutional review board.

Proofread, proofread, proofread! The investigator should go through the research plan and grant application and double-check for spelling and grammar errors and to ensure that formatting requirements for the application have been met, such as the page limits, font size, margins, spacing and section headings. Using the active voice, simple sentences and irredundant words and phrases will make the research plan and application easier to understand. It is also useful to have a trusted colleague or someone who has been successful in obtaining a grant to offer advice and guidance. In today's competitive grant world, it is likely that your grant might not be accepted on the first try, therefore, it is important to be persistent and to keep trying. The chances of getting a grant may be slim, but your chances of getting a grant will be zero if you do not apply for them!

4. Understanding how agencies select grants for awards

In today's environment of tight funding, it has become more important than ever to understand how the review process works. Reviewers are the gatekeepers to an agency's funding, as they help the funding agency decide which grants will be supported. They do this by providing an expert and impartial evaluation of the science presented in the grant proposals. In this process, the reviewers evaluate the importance of the research questions and whether they addresses a gap in the proposed scientific area, whether the proposal

could deliver on its promise to fill the gap, whether the proposed methodologies are sound and doable, and, most important, if the research has potential impact on public health or other scientific field. For example, reviewers at the National Institutes Health are asked to evaluate grants based on five impact-related factors: the significance of the science, the investigator's ability to do the science proposed, the innovation of the project, the proposed approach, and the environment where the science project will be conducted. The scientific reviewers put in a tremendous amount of effort to ensure that the funding agency is supporting the best science.

Understanding the review process

Most scientists in developing countries have very little knowledge about the scientific review process and therefore have very little information on how to write their grants to please the reviewers. It is important to understand how to present your science to the typical reviewer and how the review process works.

The typical reviewer is a scientist who is a recognized expert in his or her field; leads a laboratory of graduate students and postdoctoral fellows in training; is responsible for other laboratory staff; writes grants, manuscripts and other publications on very tight deadlines; sits on a few administrative committees at his or her institute; is a lecturer to undergraduate and graduate students at his or her institution; and is trying to balance professional life with personal life. In other words, reviewers are extremely busy and the time that they dedicate to reviewing your grant will be extremely precious to them. Remember that this typical reviewer will review and write critiques not just for your grant but for all the other applications assigned to him or her. Even though they will have approximately four to six weeks to review a grant, they probably may only do so in the week before their critiques are due. There are several ways in which you could annoy the reviewer and affect his or her enthusiasm for your grant. Reviewers are often frustrated by:

- (a) typographical errors, incomplete sentences, incorrect citations, and inconsistent format, font or heading styles;
- (b) too many acronyms, abbreviations or jargon;
- (c) lack of white space on an application;
- (d) illegible figures, tables or charts;
- (e) too many specific aims;
- (f) a dissertation-like background section;
- (g) preliminary data that do not support the research question or hypothesis;
- (h) too many subsections in the proposal.

Avoid making these mistakes. You want to make sure to present your science in a way that will convey your enthusiasm and make the reviewer an advocate for a grant. You can do this by:

- (a) presenting clear and compelling logic for doing the proposed research;
- (b) thinking logically about the anticipated problems that could arise and proposing alternative approaches;
- (c) describing the expected product from the investment;
- (d) making the application reviewer friendly by following the instructions and being neat, clear, accurate and concise;
- (e) targeting your writing to qualified scientists in the field.

Now that you understand how to write to please a reviewer, let us take a look at how the actual review process works. We will use the review process at National Institutes of Health as an example, which also is the

process most scientific reviews of proposals follow. It is always best to talk to programme officers about how reviews are conducted at their agency.

The National Institutes of Health has several standing panels that review grants based on the scientific area. A typical review panel will consist of 10 or more reviewers who are known for their expertise in the scientific area covered by their panel. The review panel is usually selected by a scientific review officer. The review officer is not the programme officer but does oversee the actual review process and has responsibility to communicate with the reviewers and assign the grant applications to the appropriate reviewers for critique preparation and assignment of scores.

Each review panel receives 80 to 100 applications. About three to four reviewers are assigned to each application. This means that each reviewer could be assigned approximately 16 applications and will serve as the primary or lead reviewer for about one-third of those assignments. Reviewers will read their assigned grants, prepare a written critique and assign an initial score based on the critique. These scores and critiques are then sent to the scientific review officer to review before the in-person review meeting. During that meeting the reviewers discuss only the top 50% of the grants with the most favourable critiques. In general, grants are discussed in the order of their initial ranking, and during the discussion the reviewers may present arguments that may affect enthusiasm for the proposal. Once the discussion is completed, the grants are assigned a final score, which may differ from the initial score. It is important to note that not all the reviewers will read your grant. Most reviewers will read the grants assigned to them but probably only the abstract of the grants assigned to other reviewers. This is the reason it is important to have a great abstract.

The secret to receiving a positive review critique is to turn the reviewer into your advocate! This can be done by writing your grant with the reviewer in mind. Do not make the reviewer's work to review your grant harder than it should be.

Revising and resubmitting the application

Reviewers are excited to be part of the review process. They get thrilled about the possibility of reading outstanding science and helping the next "big thing" to move forward. Reviewers put in quite a bit of work reviewing applications. They will provide their expert advice on the weak areas that they believe should be addressed. This will create a proposal in which the science will be strong and ensure that you are equipped to address the proposed research question. So, nothing makes reviewers more frustrated than an applicant who disregards their hard work by not following the advice they provide. Although there will be times when the reviewer may misunderstand some aspect of your proposal, if all the reviewers in the panel come up with the same critique, then you should implement the suggested changes.

Funding agencies will provide you with a summary of the critiques for your grant. Read these critiques carefully and try to understand the reviewers' concerns. This will be a good time for you to contact your programme officer as he or she most likely witnessed the discussion of your grant during the review meeting, that is if your grant was discussed. However, the rules of confidentiality of the review process will prevent the programme officer from telling you what was written in the summary statement. In addressing the reviewers' statements do not show sarcasm or contempt. For example do not say "they did not understand this technique as it is new and sophisticated". Instead, thank the reviewers for taking the time to read your proposal and then proceed to address the concerns in a respectful manner. If you agree with the reviewers, state so clearly in the reply and indicate what changes will be made. If you do not agree with their comments state why and make sure that the arguments you present are strong and will persuade the reviewers. It is also advisable to highlight any changes that you make to the application in boldface or underlining. Some funding agencies may allow you to revise and resubmit your grant more than once, but for the National Institutes of Health the first revision will be your last chance to make a case for support for the science research proposed in the grant application.

5. Grants management

Congratulations, you got the funds! Receiving the notice that a proposal will be funded is cause for celebration. At this point, you might think that the hard work is over and that you can relax and just concentrate on “doing the science”. This could not be further from the truth. Unfortunately, very few investigators are trained in the art of grant management. Effective grant management is needed for adequate oversight and monitoring of grant awards. The skill to do this is essential to set up a system of accountability while ensuring that the scientific goals of the funded proposal are accomplished. Demonstrating the necessary skills for managing the grant will provide the funding agency with evidence of your ability to manage any future funds that may come from them, whether these funds are connected to the current or a future grant.

Effective grant management begins before the award is received. In most cases you will have an idea if or not your proposal will be funded based on the critiques you received for your grant application. For example, summary critiques from the National Institutes of Health usually have an overall score for the grant that may indicate that the application is likely to receive monetary support. If this is not clear, you can ask your programme officer if there is probability that your proposal will be funded. If the chances of funding seem good, you should begin to take the first steps to manage your grant. Most of these will be administrative issues and will include management of personnel who will be working on the grant; ordering of equipment and supplies for the study; organizing laboratory, study or office space; and organizing for the collection and management of data (see Table 1).⁽²⁾ This process could be complicated, as you do not want to spend the money before you have actually received it. However, at the very least you should prepare a draft of the initial plans if you do not feel comfortable making financial commitments before receiving official notification of funding. You should also check with the funding agency to determine if any additional paperwork is required. For example, some agencies require that investigators present a list of previous and current funding for other projects to ensure that there will be no funding overlaps between those projects and the one to be funded.

Table 1: Administrative grant management checklist

| Research component | Tasks |
|----------------------------|--|
| Personnel | <ul style="list-style-type: none"> • Determining the type of personnel needed • Preparing descriptions of personnel duties (job descriptions) • Setting personnel wages • Hiring the personnel—posting the positions, interviewing applicants, setting starting dates, etc. • Performing orientation of new personnel to ensure that they are familiar with the project and administrative policies • Updating letters of agreement between investigators and agencies |
| Equipment and supplies | <ul style="list-style-type: none"> • Re-evaluating equipment needs—are there more affordable versions or newer versions, etc.? • Evaluating manufacturer’s specifications • Installation and testing the equipment • Training personnel to use and maintain the equipment • Ordering the right supplies—price checking and comparisons |
| Space | <ul style="list-style-type: none"> • Preparing the work space for the personnel—offices, laboratory space, sitting arrangements, etc. • Preparing the space for equipment—laboratory equipment, computers, etc. • Readying storage space for office and laboratory supplies |
| Institutional review board | <ul style="list-style-type: none"> • Submitting the proposal for approval by the institutional review board • Addressing any concerns relating to human subjects or other ethical issues raised by the review |
| Data management | <ul style="list-style-type: none"> • Re-evaluating the data analysis plan • Determining if additional questions will be addressed within the scope of the grant • Organizing data sets—determining which variables are needed, defining systems and processes for coding manuals, data cleaning, treatment of missing data, etc. • Ensuring appropriate personnel are trained on data management • Determining how data will be evaluated to ensure they are of good quality |

In general, starting to plan before receiving the funding will help to ensure the smooth transition of the grant as well as to keep the study on target once the award is received. Other important aspects of grants management include understanding the terms of the award, managing the budget and reporting on the progress of the study.

Understanding the terms of award

Generally, funding agencies award grants for proposals that support their mission. Therefore, you should not be surprised that these agencies have policies and rules that will need to be followed if they award your grant. Most agencies will provide you with the terms of the award. In the case of the National Institutes of Health this is called a notice of award or notice of grant award. It is your responsibility to understand and comply with the conditions and policies of the award. You should contact your programme officer if you have any questions regarding the award notice, as you will need to ensure accurate management and oversight of the project and to avoid mismanagement of the funds.

A typical notice of award will have information on the type of grant, the name of the agency awarding the grant, the title of the grant, the lead investigator's name with his or her affiliation, the budget with dates of the project period, the amount awarded in the first year, and the terms of the award. Check the terms of the award for restrictions on how the funds will be used. These restrictions may be permanent and part of the agency's policies or temporary and require some action on your part to have them lifted. For example, a restriction may be placed on the award if the funding agency believes that the recipient of the award did not adequately deal with the protection of the human subjects to be used in the study. It is imperative that you act immediately to address these types of restrictions, as not doing so will most likely delay the start of the award and, in turn, your study.

You should also be knowledgeable about which project or proposal changes you can make independently and which will require prior approval of the funding agency. The National Institutes of Health allows investigators to carry over monetary balances from a previous funding year if the amount is less than 25% of the budget of the new funding year, but they need to seek permission for amounts higher than that. Knowledge of these requirements will reduce problems that could arise from not adhering to the funding agencies' policies.

Managing the budget

Managing the budget is essential to ensure that project expenses remain within their budget limits. You should keep track of your expenditure to ensure that you maintain the appropriate documentation should an audit be performed. It is advisable that you perform a monthly review of expenditure during the funding period for the grant, as this will help to ensure that you are spending at the right pace and you will have sufficient funds to carry out all the necessary work for successful achievement of the scientific aims of the grant. Budgets for funded proposals are usually reported to the funding agency annually, and so you should become familiar with the financial reporting requirements. Most funding institutions in the United States have an established grants management office that helps investigators to keep track of their finances and that is a valuable resource for advice and guidance on proper management of budgets. This may not be the case for most institutions in developing countries. In such cases it may be advisable to hire a financial planner who has experience in grant funding. This personnel position could be written into the budget of the grant.

Reporting your progress

Most funding agencies will require progress reports at certain intervals during the funding period of the grant. Accurate reporting of scientific progress is an integral part of the grants management process, as these reports are used by funding agencies to ensure that you are meeting your scientific goals in a timely fashion. As such, the progress report serves as part of the funding agency's evaluation to determine if funding for the project should continue in the subsequent years. In some cases, programme officers will check the previous years' progress report to ensure that there are not any discrepancies between the current and past reports, so it is imperative that you present an honest assessment of your progress. Do not magnify your progress! If you encounter problems that hinder your scientific productivity, clearly outline the problem and state the steps that you will take to resolve it and to get back on track. Programme officers do understand that obstacles occur along the way that might affect scientific progress and so they appreciate the fact that you

are taking the time to address them. They can also provide advice or assistance on how to tackle issues that may be unfamiliar to you.

The requirements for the project reports will include a summary of the progress of the research funded, scientific findings, publications or presentations of the work, summary of budget expenditures, and the goals or objectives for the following year or funding period. Some agencies will also require you to state if there are any changes in key personnel or level of effort of the personnel on the grant. Be sure to take extreme care in reporting your scientific progress.

6. Summary

Understanding the grants process is essential for a successful scientific career. The process is complex, but this chapter should be a good place to start to learn the basics of science planning and grant writing. Writing research grants is not innate but it is an art that can be learned. Understanding how the review process works will help you to develop the skills and will provide pointers that will strengthen your grant. In addition, make sure that you develop a close network of colleagues and collaborators who will not only help you to improve your grant skills but who will also be able to offer advice and guidance on management of your grant. You can do it!

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1. Porter R. Can we talk? contacting grant program officers. *Research Management Review*, 2009, 17(1):10–17.
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4. Bergstrom N, Baun MM. The proposal-reality gap: the mechanics of implementing a funded research proposal. *Nursing Outlook*, 1994, 42(6):272–278.

Appendix

NIH grants process for international scientists

The National Institutes of Health (NIH), a part of the US Department of Health and Human Services, is the largest medical research funding agency in the world. Consisting of 27 institutes and centres (ICs) with specific research areas, the NIH provides researchers and institutions the opportunity to competitively apply for research and training opportunities in the US and internationally.⁽¹⁾

NIH has specific funding opportunities for international principal investigators and institutions. In a few cases there are also funding opportunities specifically for research collaborations between US and international scientists. NIH's Office of Extramural Research (OER) provides the leadership, oversight, tools and guidance needed to administer and manage NIH grants policies and operations.⁽²⁾

Before applying for NIH funding

Institutes whose investigators will be applying for NIH funding must be registered on the Grants.gov web site to be able to submit their applications. Grants.gov was established to allow for electronic submission of grant applications and also to act as the storehouse for information on over 1000 grant programmes. The registration process can take up to a week and the investigator's institute does not have to wait until the investigator is ready to submit an application. It is advisable that all institutes start this process. Registering at Grants.gov also allows institutes to reach all US federal agencies that would be of interest to investigators within their institute. For more information on this process, visit http://www.grants.gov/applicants/apply_for_grants.jsp.

Types of programmes

With all the exciting NIH research opportunities to apply for, which ones are appropriate for international investigators and institutions? Investigators need to understand how NIH categorizes grant funding opportunities and should closely read the funding opportunity announcement to verify their eligibility. The main categories are research grants (R series), career development awards (K series), research training and fellowships (T and F series), programme project/centre grants (P series), resource grants (varied series), and Trans-NIH programmes.⁽³⁾

The R awards offer several opportunities for international researchers and institutions:⁽⁴⁾

NIH Research Project Grant Program (R01). R01 is the oldest NIH grant mechanism, supporting health-related research if the researcher's interest aligns with the NIH mission. Applications for R01s can be in response to a funding opportunity announcement or initiated by the investigator. Unless indicated in the announcement, R01s do not have a specific funding limit; however, the funding requested should reflect the needs of the project. R01s are awarded for three to five years and are open to renewal. All NIH institutes and centres offer R01 grants.

NIH Small Grant Program (R03). R03 is intended for small research projects with a short time frame and limited resources. Examples of eligible projects include pilot or feasibility studies, preliminary data or secondary data analyses and new research technology. R03s are limited to two years of funding and budgets of up to two modules of US\$ 25 000 or one module of US\$ 50 000 per year. R03s are not renewable. Certain NIH institutes and centres do not accept investigator-initiated R03 grant applications, but might make funding opportunity announcements specific to their research area.

NIH Exploratory/Developmental Research Grant Award (R21). R21 supports early stages of new exploratory and developmental research projects. R21s are limited to two years of funding and direct costs budgets of up to US\$ 275 000. R21s are not renewable. Certain NIH institutes and centres do not accept researcher-initiated R21 applications but might send out funding opportunity announcements for R21s specific to their research area.

NIH does not fund investigators in international institutions for the certain activity codes (4): R13/U13—support for conferences and scientific meetings (the meeting may be held at an international location but the grantee must be a US-based institution); R41/42—small business technology transfer (STTR); R43/44—small business innovation research (SBIR); and K awards. One exception is K99 (NIH pathway to independence award). The goal of this award to provide young investigators with grant funding to allow them to transition from a mentored to an independent position. These are five-year awards with funding split into two phases. The initial phase funding is used during the first two years of mentorship. During that time the awardees work on research programmes that they will eventually take into their independent position. The second phase of the award allows the investigator to continue to develop the research programme and gather the preliminary data that will be used to apply for R01 funding. More information is available at <http://grants.nih.gov/grants/guide/pa-files/pa-07-297.html>.

Does NIH have activity codes specifically for international investigators and institutions? Yes! The following list includes international activity codes (4):

- (a) International Research Training Grants (D43): D43s support research training programmes for US and international investigators to strengthen global health research and international research collaboration.
- (b) International Research Fellowships (F05): These provide collaborative research opportunities for qualified international investigators who hold a doctoral degree or its equivalent in biomedical or behavioural sciences.
- (c) Extramural Associate Research Development Award (G11): G11s fund eligible institutions to participate in the NIH Extramural Associates Program for establishing or strengthening an office to support sponsored research, or other research infrastructure needs.
- (d) Minority International Research Training Grants (T37): T37s are institutional training grants awarded to domestic institutions offering opportunities for biomedical and behavioural research training for minority students and faculty members at foreign sites.
- (e) International Cooperative Agreements (U2R/U2G): U2R/U2G cooperative agreements support training, capacity building, international research collaborations and/or HIV/AIDS prevention.
- (f) R Awards for International Researchers and Institutions.

Specific NIH R support for international researchers and institutions (4):

- (a) Fogarty International Research Collaboration Award (FIRCA): FIRCA is an R03 award supporting research collaborations of NIH-supported scientists and international investigators in developing countries.
- (b) Global Research Initiative Program for New Foreign Investigators (GRIP): Using the R01 activity code, GRIP supports NIH-trained international scientists (postdoctoral scientists or recent graduates) to establish research programmes in their home countries.
- (c) International Research in Infectious Diseases including AIDS (IRIDA): IRIDA is an R01 award for international investigators in developing countries to study infectious diseases that are of interest to their country.

- (d) International Research Collaboration on Drug Abuse and Addiction Research: This programme supports research collaborations between the US and other countries on drug abuse and addiction using the R01, R03 and R21 activity codes.
- (e) International Research Ethics Education and Curriculum Development Award: This R25 award supports international institutions to develop master's level curricula and educational opportunities in ethics and human subjects for developing countries.
- (f) D43, F05 and G11 Awards for International Research and Institutions.

NIH has other research and training opportunities using D43, F05 and G11 activity codes (4):

- (a) Fogarty HIV Research Training Program (formerly the AIDS International Training and Research Program or AITRP): This is a D43 programme that supports US-based training for international principal investigators from developing countries to strengthen HIV-related and public health capacity in their institutions.
- (b) Global Infectious Diseases Research Training Program Award: This D43 programme enhances the knowledge and skills of principal investigators and health professionals from developing countries to conduct infectious diseases research. This award does not include HIV/AIDS research.
- (c) Millennium Promise Awards: Non-communicable Chronic Diseases Research Training Program: This is a D43 programme for research capacity building in developing countries for noncommunicable diseases and health concerns such as cancer, cerebrovascular disease, lung disease, obesity and lifestyle factors.
- (d) International Neuroscience Fellowship: Using a F05 activity code, this fellowship enhances the basic, translational or clinical research skills in a US research setting for early or mid-career international neuroscientists and clinicians.
- (e) International Extramural Associates Research Development Awards (IEARDA): IEARDA is a G11 programme that trains academic research administrators in developing countries to build or enhance research administration infrastructure in their home institutions.

Final thoughts

Applying for NIH research and training support, especially as an international investigator, is competitive but not impossible. Principal investigators should develop a unique and innovative research project and effectively plan ahead. They should keep in mind that since NIH is a US agency, their proposed research project should have a US and international benefit. Also, investigators should carefully read NIH funding opportunity announcements to verify their eligibility, since not all of NIH opportunities are open to international investigators. Contacting the programme officer listed on the announcement is encouraged.

The NIH Office of Extramural Research is a great resource for information on programme announcements, application requirements, grants process and policies, and grant-related forms. This office also offers webinars and seminars for education on the NIH grant process and interaction with NIH and the research community at large.

Resources

1. The National Institutes of Health (<http://www.nih.gov>, accessed December 2012).
2. *NIH grants and funding* (<http://grants.nih.gov/grants/oer.htm>, accessed December 2012).
3. *NIH grants and funding activity codes* (http://grants.nih.gov/grants/funding/ac_search_results.htm, accessed December 2012).
4. *NIH foreign grants—foreign specific programs* (http://grants.nih.gov/archive/grants/foreign/foreign_specific.htm, accessed December 2012).
5. *The NIH grant review process reviewed* (<http://www.youtube.com/watch?v=fBDxI6I4dOA>.)
6. *NIH tips for applicants* (<http://www.youtube.com/watch?v=9cNRMscGfHo>)

SECTION II: CONDUCTING RESEARCH

Chapter 6

Community engagement research: principles and best practices for Africa

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Chapter outline

1. Introduction: community engagement research defined
2. Operationalizing CEnR: shared leadership level
3. Defining the community
4. Best practices for community engagement
5. Practical Steps for CEnR as demonstrated in the CBPR project in Nigeria
6. Community engagement from an African perspective: the Khayelitsha case study, South Africa
7. Conclusion

1. Introduction: community engagement research defined

“If the problems are in the community, the solutions are in the community.” To develop tailored and targeted cancer prevention and control interventions that are responsive to the needs of African communities, it is important that the community be part of the solution to the cancer problem in Africa. It is now well recognized globally that the traditional way of conducting research without involving the community has not been successful in addressing community-health or public-health problems. Since cancer prevention and control occur at the level of the community, community engagement research (CEnR) has become the focal approach for researchers to discover practical solutions to improve human health.

CEnR encompasses both research scholarship and community engagement (CE). CEnR goes beyond the traditional unidirectional academic framework of generating and applying knowledge in communities, or the “expert model”, to bidirectional research collaboration of the academic institution and the community. This makes the CE piece of CEnR very important. According to the United States Centers for Disease Control and Prevention (CDC), CE is “the process of working collaboratively with and through groups of people affiliated by geographic proximity, special interest, or similar situations to address issues affecting the well-being of those people”.⁽¹⁾ It is characterized by community involvement in all aspects of the research, including research assessment, access to information, decision-making and capacity building for advocacy, and by the academic institution’s accountability to the community.⁽²⁾

CEnR is an approach to conducting research with community involvement in all phases of the research, including development of the research objective and the study design; participant recruitment and retention; instrument design; and data collection, analysis, interpretation and dissemination. CEnR requires a partnership between the academic institution and the community and exists on a continuum, with its intensity depending on how the community is involved in the research. The level of community involvement increases from community outreach to shared leadership, as summarized in Table 1.⁽³⁾ The ideal is a 50–50 partnership between the academic institution and the community, as exhibited in the shared leadership model.

Table 1: Levels of community involvement⁽³⁾

| Outreach | Consult | Involve | Collaborate | Shared leadership |
|---|--|--|---|---|
| Some community involvement | More community involvement | Better community involvement | Community involvement | Strong bidirectional relationship |
| Communication flows from one to the other to inform | Communication flows to the community for answer seeking and then back to project | Communication flows both ways in a participatory form | Communication flow is bidirectional | |
| Project provides community with information | Project gets information or feedback from community | Project involves more participation with community on issues | Project forms partnerships with community on each aspect from development to solution seeking | Final decision making is at community level |
| The entities coexist | The entities share information | The entities cooperate with each other | The entities form bidirectional communication channels | The entities form strong partnership structures |
| Outcomes: Optimally established communication channels and channels for outreach | Outcomes: Connections developed between entities | Outcome: A partnership with improved cooperation | Outcomes: Partnership and trust | Outcomes: Broader health outcomes affecting the broader community and strong bidirectional trust |

2. Operationalizing CEnR: shared leadership level

A well-known CEnR framework that is based on shared leadership is the community-based participatory research (CBPR) approach. According to the WK Kellogg Foundation Community Health Scholars Program⁽⁴⁾ CBPR is “... a collaborative approach to research that equitably involves all partners in the research process and recognizes the unique strengths that each brings. CBPR begins with a research topic of importance to the community and has the aim of combining knowledge with action and achieving social change to improve health outcomes and eliminate health disparities”.

The primary aim of CBPR is to “enhance understanding of a given phenomenon and the social and cultural dynamics of the community, and integrate the knowledge gained with action to improve the health and well-being of community members”.^(5,6) This means that researchers have to change their traditional way of conducting research to include “the researched” people as partners, in order to effectively improve their health or their health systems, programmes or policies. The analytical framework proposed for CBPR is summarized in Figure 1.⁽⁷⁾ Without any doubt, fully involving the researched people as members of the research team does not benefit only the community but also the researchers. In addition to improving the health and well-being of the community, CBPR generates certain advantages:⁽⁵⁾

- (a) The quality, validity, sensitivity and practicality of the research are enhanced since local knowledge from the participants is exploited.
- (b) The relevance and usefulness of the research data are enhanced for all the partners.
- (c) Addressing of complex problems can be effectively facilitated when partners with diverse skills, knowledge and expertise work together.
- (d) The research and programme development capacity of the partners is strengthened.

- (e) The trust of the community in the researchers is improved.
- (f) Community members receive a financial gain with the funding for the research and employment opportunities related to the research.

Figure 1: Analytical framework for CBPR⁽⁷⁾

| Research steps | Traditional research component | Community-based participatory component (CEnR) |
|---|--|--|
| Health concern identified | Issues identified based on epidemiologic data and funding priorities | Full participation of the community in identifying issues of greatest importance → Benefit: <i>Increased motivation to participate in the research process</i> |
| ↓ | | |
| Study designed and funding sought | Design based entirely on scientific rigor and feasibility; funding requested primarily for research expenses | Community representatives involved with the study design and proposal submission → Benefit: <i>Increased acceptability of the study approach. Funds for community costs should be included</i> |
| ↓ | | |
| Participants recruited and retention systems implemented | Approaches to recruitment and retention based on scientific issues and “best guesses” to reach community members and keep them involved in the study | Community representatives provide guidance on recruitment and retention strategies → Benefit: <i>Enhanced recruitment and retention</i> |
| ↓ | | |
| Measurement Instruments designed and data collected | Measurement instruments adopted or adapted from other studies and tested chiefly with psychometric analytic methods | Measurement instruments developed with community input and tested in a similar population → Benefit: <i>Potentially sensitive issues handled better and reliability and validity of measures increased.</i> |
| ↓ | | |
| Intervention designed and implemented | Researchers design intervention based on literature and theory | Community members help guide intervention development → Benefit: <i>Ensures greater cultural and social relevance to the population served, increasing the likelihood of producing positive change.</i> |
| ↓ | | |
| Data analysed and interpreted, and findings disseminated and translated | Researchers report findings from statistical analysis and publish in peer-reviewed journals | Community members assist researchers with interpretation, dissemination and translation of findings → Benefit: <i>Ensures greater sensitivity to cultural and social norms and climate, evades potential group harm and enhances potential for translation of findings into practice.</i> |

The critical elements of CEnR, including the benefits and barriers, are summarized in Table 2.⁽⁷⁾ While there are many benefits in using the CEnR framework, implementing the framework can generate challenges for researchers especially in Africa. This is related to the resource gap between academic institutions and communities where the research is conducted, which is much wider than in industrialized countries.

Table 2: Critical elements of CBPR⁽⁷⁾

| Research element | CBPR application | Community benefits | Research benefits | Research challenges |
|--|---|--|---|--|
| Assembling a research team of collaborators as potential members of a research partnership | Identifying collaborators who are decision- makers and who can move the research project forward | Resources can be used more efficiently | Increases the probability of completing the research project as intended | Finding time to identify the right collaborators and convincing them that they will play an important role in the research project |
| Creating a structure for collaboration to guide decision- making | Consensus on the ethics and operating principles for the research partnership to follow, including on protection of study participants | The beginning of trust building. Increases the likelihood that procedures governing protection of study participants will be understood and acceptable | An opportunity to understand each collaborator’s agenda, which may enhance recruitment and retention of study participants | An ongoing process throughout the life of research partnerships that requires skills in group facilitation, building consensus and conflict accommodation |
| Defining the research question | Full participation of the community in identifying issues of greatest importance; focus on community strengths as well as problems | Problems addressed are highly relevant to the study participants and other community members | Increased investment and commitment to the research process by participants | Time consuming as the community may identify issues that differ from those identified by standard assessment procedures or for which funding is available |
| Grant proposal and funding | Community leaders or members involvement as a part of the proposal writing process | The proposal is more likely to address issues of concern in a manner acceptable to community residents | Funding likelihood increases if community participation results in tangible indicators of support for recruitment and retention efforts, such as writing letters of support, serving on the steering committee or as fiscal agents or co- investigators | Seeking input from the community may slow the process and complicate the proposal development effort, which often already has time constraints issues to deal with |
| Research design | Researchers communicate the need for specific study design approaches and work with the community to design more acceptable approaches, such as a delaying the intervention for the control group | Participants feel they are contributing to the advancement of knowledge instead of serving as passive research “subjects”, and they believe that a genuine benefit will be gained by their community | The community is less resentful of the research process and is more likely to participate | The design may be more expensive or take longer to implement than if the community was not that involved. This might pose possible threats to scientific rigor. |
| Participant recruitment and retention | Community representatives guide researchers on the most effective way to reach the intended study participants and to keep them involved in the study | Those who may benefit most from the research are identified and recruited in a dignified manner rather than made to feel like research subjects | Participant recruitment and retention are facilitated, which are among the main challenges in health research | Recruitment and retention approaches may be more complex, expensive or time consuming |
| Formative data collection | Community members provide input to intervention design and identify barriers to recruitment and retention of participants etc. via focus groups, structured | Interventions and research approach are likely to be more acceptable to participants and thus of greater benefit to them and the broader | Service-based and community-based interventions are likely to be more effective than interventions designed without | Findings may indicate needed changes to proposed study design, interventions or timeline, which may delay progress |

| | | | | |
|---|--|--|---|---|
| | interviews, narratives or other qualitative methods | population | prior formative data collection | |
| Measurement instrument design and data collection | Community representatives are involved in extensive cognitive response and pilot testing of measurement instruments before formal research begins | Measurement instruments are less likely to be inappropriate or confusing to participants | Quality of data is likely to be superior in terms of reliability and validity | Time consuming with possible threats to scientific rigor |
| Intervention design and implementation | Community representatives are involved in selecting the most appropriate intervention approach, taking into account the cultural and social factors and strengths of the community | Participants feel the intervention is designed for their needs and offers them benefits while avoiding insult. The study provides resources for the community's involvement | Intervention design is more likely to be appropriate for the study population, increasing the likelihood of study success | Time consuming; hiring staff locally may be less efficient than using outside staff hired for the project |
| Data analysis and interpretation | Community members are involved to provide their interpretation of the findings within their local social and cultural contexts | Community members who hear the results of the study are more likely to feel that the conclusions are accurate and sensitive | Researchers are less likely to be criticized for limited insight or cultural insensitivity | Interpretations of data by non-scientists may differ from those of scientists, calling for thoughtful negotiation |
| Manuscript preparation and research translation | Community members are included as coauthors of the manuscripts, presentations, newspaper articles, etc., following previously agreed-upon guidelines | Pride in accomplishment, experience with scientific writing, and potential for career advancement; Findings are more likely to reach the larger community, and potential for implementing or sustaining recommendations is increased | The manuscript is more likely to reflect an accurate picture of the community environment of the study | Time consuming and requires mutual learning and negotiation |

3. Defining the community

MacQueen et al. ⁽⁸⁾ define a community as “a group of people with diverse characteristics who are linked by social ties, share common perspectives, and engage in joint action in geographical locations or settings”. Four perspectives are commonly used in defining a community (3):

- (a) Individual perspective: This is based on how a person sees himself or herself and how he or she is seen by others. It is interesting that in some cases an individual’s self-perception is not necessarily congruent with the way others see him or her. What is important in CEnR is self-perception. The researcher must make the effort to understand the perceptions of the individual relative to his or her identity, connections with others and how he or she enters into relationships with others.
- (b) Virtual perspective: The advancement in social media such as Facebook, Twitter, YouTube, Skype and Instagram has led to the growth of numerous “virtual communities” and creation of a virtual perspective. These virtual communities can be actively engaged for cancer prevention and control activities nationally and internationally. The primary advantages of virtual communities are their instant access by researchers and the ease of their use in sharing cancer information.

- (c) Social perspective: This perspective describes the connection of individuals through social and political networks. The social community comprises individuals, community organizations and leaders.
- (d) Systems perspective: The systems perspective recognizes the different systems that exist within a community, such as education, political environment, health and transportation, that all operate within well-defined boundaries. For example, the educational system operates separating from the health system. However, it is important that these systems work effectively and synergistically to foster health in the community.

Regardless of the community perspective, five core elements define communities: locus, sharing, joint action, social ties and diversity. ⁽⁸⁾ Locus describes the physical location or place where the community is based, for example a specific area such as the village, a specific setting such as work place or a general location. The sharing element refers to the shared perspectives and interests that create the sense of community such as cultural beliefs and values, physical attributes and history. Joint action generally refers to the bringing of people together to create a sense of community, for example when people socialize in the same club, worship in the same church or volunteer at the same health event. The element of social ties is concerned with the foundation around which the community is built, for example interpersonal relationships such as family and friends. The diversity element refers to the social complexity within a community, for example sociodemographic differences such as race, ethnicity, marital status, educational level and socioeconomic status.

The first step in CEnR is to define the community. A comprehensive understanding of the community with the cancer health problem being targeted is very important. In identifying the community, special consideration should be given to cancer patients as well as individuals who have experience with cancer such as cancer survivors, caregivers and advocates.

4. Best practices for community engagement

Successful community engagement requires challenging the traditional and often institutionalized policies and beliefs about the relationship between the researcher and the community. It also requires a personality style that is characterized by thoughtfulness, common sense and perspicaciousness. This keen sense of awareness and sensitivity is probably the hallmark of a good community-engaged individual. The valued approaches we present below facilitate establishing of good relationships between researchers and the community in which they work.

Respect of person

Community-engaged research, as all research, requires that investigators and community respect one another. The investigator, who wants something from the community members, should show respect at the first interaction, and the community will naturally reciprocate. Respect for people, defined as mutual admiration or thoughtfulness, is a quality we aspire to but often do not achieve. It is one of three core principles—the other two being beneficence and justice—that we must adhere to as investigators according to the Belmont Report⁽⁹⁾ from the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. The three principles should serve as our guide in the evaluation of all research to avoid ethical problems from such research. Though relatively recent in history, the Belmont Report is now used around the world to ensure proper treatment of humans in research.

The process of learning to show respect for research participants requires that we first acknowledge that historically there have been significant exploitation and paternalistic tendencies associated with human subject research. In fact, around the time of the creation of the Belmont Report there was great tension between medical schools and communities in which they were conducting research, as the medical schools were seen to be more interested in the physical plants and buildings than in respecting the communities they

worked in. Often research institutions were situated in low-income urban settings and involved the community very little in the decision-making associated with the research, and the communities often were not the beneficiaries of the great improvements that came from the research. More money and time were focused on the physical plant than on the health of the community the institution served.⁽¹⁰⁾ That, coupled with the history of unethical treatment during the United States Tuskegee Study, left people, especially US blacks, fearful and mistrustful of science and scientists.⁽¹¹⁾

As scientists, we must be clear about our goals and expectations and respectful of the community who will be involved. The research scientists can facilitate this by developing norms that their team must work by and ensuring that these are not violated. The Belmont Report proposes guidelines consistent with such norms: that the person enters into the research voluntarily and without coercion and that this principle be upheld through respect. It also means that we must be good stewards of the findings as well, and advocate for bidirectional flow of scientific findings to include the community on which the research was conducted. Something as small as allowing members of the community advisory board to help plan the meeting agenda was perceived as an indication that the community was respected.^(12,13)

Give people a chance to tell their story

In a recent study in five US Clinical and Translational Science Awards (CTSA) sites across the country, where community health workers assessed health concerns, conditions and research perceptions of traditionally underrepresented groups, Cottler et al.,⁽¹⁴⁾ through this CTSA Sentinel Network, found that approximately 87% of community members were interested in participating in research, with highest rates being reported by African Americans. Despite this, less than 2% of the population participates in studies.⁽¹⁵⁾ Groups traditionally underrepresented in research include women, the elderly, racial or ethnic minorities, and rural populations.^(16,17) This discrepancy indicates a need to reach out to these populations and remove barriers to research participation among them. What is important to the community? What are their health concerns and conditions? Including underrepresented populations, for example populations from rural communities, in research is not only necessary in building trust between researchers and the community but is also integral to maintaining the external validity of the research findings.

Our work with the Sentinel Network study clearly demonstrates that a high proportion of participants among the nearly 6000 treatment community members who participated in our assessment were interested in participating in the research and had clear ideas about the kinds of research in which they would be willing to participate. Across all sites participants said they would most likely participate in a study that is non-invasive and that does not require hospital stay, medical equipment or medication. These questions at first were not included in the study because the team felt they might not be understood or would cause discomfort. They turned out to be very important for discovery of perceptions that people have, and our findings have made a significant contribution to the field.

Narrative interventions are a strategy used to gain information from people, and have been employed in public health, nursing and medical research on eliminating cancer disparities and hypertension. Studies have shown that survivor story interventions can be used to highlight emotional reactions to cancer diagnosis, survival and treatment.⁽⁸⁻²⁰⁾ In a study of 10 to 18 year olds, we asked questions about stimulant use and questions that required data on age or usage. At the end we asked the participants to tell us how, if they were in charge of the world, they would stop their friends from using other people's prescription drugs. The group was fascinated with the question and gave us very interesting information that could be useful in preventing an epidemic of prescription drug misuse.

Confront unconscious bias

Everyone has unconscious biases, even though we as scientists pride ourselves in our objectivity. There is wide literature on the influence of unconscious assumptions and biases. Studies on the influence of unconscious bias include those on height and weight influences, gender bias in letters of recommendation, skill levels attributed to men, and sports attributes and race. Campaigns have been organized to have women teach at academic institutions about overcoming these biases, especially as they pertain to women, but none such campaigns exist for eliminating unconscious bias relating to race and ethnicity.

The principles for eliminating unconscious bias in our research teams include raising awareness on assumptions and biases, discussing these biases with the team and asking teams to call out biases when they see them. Recently our team held discussions on our implicit biases and we realized that some of us had not ever thought about the effect their biases had on their behaviour. We uncovered the effects of these biases on scheduling of appointments, returning of phone calls, conducting of outreach activities in unfavourable weather, and how eager someone was to participate in research during certain times in the month or if their pay checks was deposited. Some team members thought that their beliefs were facts not biases. During our discussion on how these biases could affect data collection and people's perceptions of our team, we realized that these discussions needed to be repeated as often as during each team meeting.

Biases exist with investigators as well as staff members. Some investigators believe that certain populations are less desirable as respondents. For example, depressed people and people with addiction are often excluded in research.⁽²¹⁾ Blanco et al.⁽²¹⁾ found that over half of the people who met criteria for alcohol dependence would be excluded from a study. The literature is full of studies that excluded alcohol or drug users, poor or unemployed people and people with psychiatric problems such as depression. Investigators perceived such groups as being incapable of complying with the requirements of the study and not to be motivated to complete the study.⁽²²⁾ Studies conducted on methods to enrol, retain and benefit out-of-treatment drug users in intervention studies have shown great success with such groups, in fact with retention rates as high as 95% after 18 months.⁽²³⁻²⁴⁾

When we let preconceived beliefs affect our actions, we surrender our objectivity, perpetuate stereotypes and compromise research findings. While there has been deep mistrust in research, the tide may be beginning to turn. In the United States, one of the salient findings of our CTSA funded multisite Sentinel Network study indicates that African Americans report more likelihood to participate in research compared with other racial or ethnic groups, including caucasians. This pattern extended to studies in which blood and genetic samples would be drawn. This information was obtained by asking out-of-treatment individuals in laundromats, parks, bus stops, health fairs and other community places about their perceptions of research. The community health workers asked the participants about their health needs and concerns as well. We interpret this as a waning of the reluctance of African Americans to participate in medical research.

Other studies also suggest that African Americans may be more willing than other racial groups to participate in health studies and remind us again that our unconscious biases and assumptions get in the way of our work.^(25,26) In fact, they may be overrepresented in some areas of research including genetic studies.^(27,28) For example, our global studies on prostate cancer have successfully recruited Black men worldwide, including a study with over 3000 African Americans, African immigrants and Caribbean immigrants in the United States.⁽²⁹⁻³³⁾

This new willingness of respondents from all populations to participate in clinical or other health research may be the result of extra efforts of committed investigators around the world. For the first time scientists are learning what it means to listen to consumers.

Believe in the power of positive deviance

New and different approaches to solving problems are often met with doubt or even hostility when they are introduced in a top-down fashion or are perceived as “foreign”. When solutions are not from within a community or system they may be doomed to fail. The positive deviance (PD) approach is based on the belief that every community, village, corporation, institution etc. has the resources to generate successful behaviours that help produce solutions to its problems. This theory has been used in Africa to understand malnutrition, HIV/AIDS risk, neonatal mortality, and MRSA eradication and prevention.

Created by Jerry and Monique Sternin from Tufts University, the PD model treats the group as the guru or the champion of a course and involves working through change agents in the group or community.⁽³⁴⁾ The model reframes questions using facts built from reality. Groups have myths and norms that may not be correct, so the PD method reframes the problems around new ideas and new possibilities. It asks people to look at things in a new way and to go beyond treating feelings as facts. Next, the PD model makes it safe to learn new behaviours, whether these pertain to school dropout rates, food insecurity, taboos in the workplace, or a health habit like poor hand washing techniques. As the problems are concretized the community becomes active participants in the campaign to promote the new behaviour to deal with the problem. Once people see others on board, they too join in and positive change diffuses into the community. Spontaneous initiatives begin and the behaviour changes.

This model has been used to overcome barriers to interventions for many different diseases, for example the recent case of cervical cancer in the Honduras. The investigators interviewed women who were practising uncommon but beneficial practices of screening and found practices that could be useful in ensuring that women were taking care of their health.⁽³⁵⁾ This model could be used to choose community members to help make a positive change and to influence the community to understand the importance of research and new screening tools or other efforts that could improve the health of a community. At the very least, investigators should start to familiarize themselves with this approach not just for their community but for their own team members as well.

Know the community

Investigators must realize that they must first understand the needs and concerns of the communities in order to best help them. Although the United States Institute of Medicine (IOM) has published the top health concerns⁽³⁶⁾ for each community, what the community thinks is important to them, whether that community is defined by age, urbanicity, gender or race. Relying on community health workers or lay health workers can be a successful and feasible way to connect to the communities, but there is nothing more important than to have investigators to get to personally know the communities in which they work. This can be accomplished if research investigators doing outreach work with community health workers take that opportunity to connect with the community by showing respect and cultural sensitivity to the people they meet. Understanding the health needs and concerns of that population becomes critical in helping meet their needs and helping to shape the research mission for underrepresented populations. Giving people a voice in the research enterprise is one of the most important outcomes of community-engaged research.

5 Practical steps of CEnR as demonstrated in the CBPR project in Nigeria

Although the CEnR approach is relatively new and has not been widely adopted in Africa, it is an adaptable practice with potential for positive impact on cancer prevention and control programmes on the continent. A successful CEnR project in Africa was the prostate cancer research project in Nigeria conducted by members of the Prostate Cancer Transatlantic Consortium (CaPTC) in Ogun State from 2011. Dr Folakemi Odedina was the project’s principal investigator and Dr Titilola Akinremi the local principal investigator.

Project title: Prostate cancer and risk factors in black men of African ancestry

Abstract: It is disconcerting that black ethnicity is one of the three confirmed primary non-modifiable risk factors for prostate cancer. In spite of significant research on prostate health disparities between black men and white men in the United States, the disparate burden of prostate cancer in black men of African ancestry is still poorly understood. Given the genetic similarities among black men of African ancestry in both the United States and Africa, especially those connected by the transatlantic slave trade, it has become important to explore ethnic variations among black men to better understand prostate cancer etiology in their race. Using the principles of community-based participatory research (CBPR), this pilot study explored some of the biobehavioural risk factors associated with prostate cancer among indigenous black men in West African populations.

We highlight below the CBPR attributes in the CaPTC project.

Step 1: Defining the “community”

Various types of communities exist in Nigeria such as neighbourhood, professional, religious, political and trade groups, all with defined leadership and membership. The CaPTC study was carried out in the Abeokuta South Local Government Area (LGA) in Ogun State. Abeokuta South LGA is an urban community that has a population of about 250,000, based on the 2006 census. The target community for the study was identified based on a social perspective and included healthy individuals and prostate cancer patients. The target population was black Nigerian men with biopsy-confirmed prostate cancer. The control was an age-matched group of with no history of cancer.

Step 2: Identifying and selecting partners

Selecting the appropriate partner is essential for any CEnR project, whether the partner is an organization or an individual. The CaPTC study found the right community partner in Tunde and Friends Foundation (TAFF), a non-profit organization that runs a community health outreach programme in Abeokuta. TAFF is well established in Abeokuta and has the confidence of various community groups. The community’s trust in TAFF ensured success for the CaPTC study in recruitment of participants, and the community outreach programmes organized by TAFF provided appropriate recruitment sites.

Step 3: Constituting an advisory board

CaPTC has a standing community advisory board (CAB) comprising diverse membership representing black populations from Africa, the Caribbean and the United States. This board brings a community perspective to the CaPTC strategic plan, projects and programmes. Specifically the board:

- (a) Guides CaPTC activities and programmes to ensure the health needs of targeted communities are met.
- (b) Serves as a the first-level review group for human subjects to ensure that all CaPTC-supported research programmes are appropriate for targeted populations.
- (c) Provides advice on the effective approaches for health education and outreach for targeted communities.
- (d) Advises CaPTC on methods for reaching populations targeted for research.
- (e) Identifies resources within the community to support the activities of the consortium.
- (f) Promotes linkages between the diverse communities and CaPTC.

Besides the CaPTC board, each research team is also supported by a local community advisory board. The TAFF advisory board served that purpose for this study. The TAFF advisory board draws membership from the larger Abeokuta community and is composed of community leaders such as the chief, religious leaders, health workers, teachers and other lay people. CaPTC delegated to the TAFF advisory board the role of liaising directly with the community in conducting the study.

Step 4: Identifying and prioritizing the relevant issues

CaPTC members work very closely with the community to identify and prioritize health issues that need to be addressed in partnership with the community. The study problem for this project was generated within the community, which was to close the knowledge gap in the contribution of ethnicity in variations in prostate cancer burden and control among black men. On Saturday, 18 September 2004, one participant in a town hall meeting at the statewide Florida African American Men's Prostate Cancer Forum organized in the United States raised the question about why prostate cancer incidence was so high among black men. He added that he heard that the disease was not as prevalent among black men in other countries and that migration to the United States might have had something to do with it. He added with a laugh, "Maybe we should all move back to Africa". These comments led to the development of a research programme to explore and quantify the prostate cancer variance among black men globally.

CaPTC's research interest in prostate cancer and risk factors in black men of African ancestry demanded that the ethnic variations among black men be studied to better understand prostate cancer etiology. Hence the pilot study was designed to explore some of the biobehavioural risk factors associated with prostate cancer among indigenous black men in West African populations. Stakeholders, including community leaders on the TAFF advisory board, were informed of the relevance and components of the study. Community leaders understood and agreed on the importance of the study.

Step 5: Defining the research question

The research problem for the study originated from the community. In defining the research question, the researchers worked closely with the community to take into consideration the community's strengths and weaknesses in relation to the study.

Step 6: Grant proposal and funding

This pilot project was funded through intramural support from the University of Florida College of Pharmacy in the United States. For subsequent grants for the study, members of the local advisory body were heavily involved in writing the proposal, especially the sections on participant recruitment and data collection.

Step 7: Research design

The CaPTC research was designed as a multinational collaborative study to address the need to compare black men globally. The project was set up to be culturally responsive at each site, and the key personnel comprised researchers and community leaders from the sites. It was very important that the researchers worked with each community to design appropriate strategies for the study. For example, one of the researchers was interested in obtaining hair samples from the participants but when it was pointed out that this might be seen as an odd or even a fetish practice in some parts of Nigeria, hair sample collection was not included during data collection.

Step 8: Participant recruitment

TAFF provided guidance to the study team on the most effective way to recruit participants using educational activities. Recruitment announcements were made through radio jingles, television advertisements, posters and hand bills distributed within the targeted community.

At the health screening outreach programme organized by TAFF, both male and female attendees were educated on prostate cancer and the risk factors via video shows or lectures. CaPTC desks were set up to discuss the project with men during the educational sessions. Thus, prostate cancer education and screening were provided at the same time as the study was running. It was important that the research team give back to the community at the time that it was “taking” from them.



Nigeria CaPTC study participants, TAFF resource persons and the research associates at a health screening event in Abeokuta.

Step 9: Measurements, instrument design and data collection

The involvement of community representatives is very important in the development and pilot testing of the study instruments. The study instrument for the CaPTC project was developed in collaboration with community leaders in the United States including African, Caribbean and American black men. In addition, it had been validated among over 3000 black men in the United States of African, American or Caribbean birth. The instrument was revalidated in Nigeria for factors of face and content validity. It was subsequently translated into two local languages to facilitate its use and acceptability among participants who did not speak English.



Data collection during the Nigeria CaPTC study.

Step 10: Data analysis and interpretation

Data from the project are currently undergoing cleaning, and analysis has not started. As in past CaPTC projects, we will work closely with the advisory board members of both CaPTC and TAFF to interpret of the findings within the sociocultural context of the Yoruba population in Abeokuta.

Data collection during the Nigeria CaPTC study.

Step 11: Dissemination of findings

The involvement of the community in disseminating research findings is very important in ensuring that that process is appropriately carried out and in a sensitive manner. One approach that has worked successfully for us is using the “community report” to disseminate the study findings and the potential implications for cancer prevention and control in the community. Our past efforts to distribute such reports globally, for example the reports on “Prostate cancer communication: educating African-American men: do’s & don’ts” and “Do black men’s health and cultural beliefs affect prostate cancer prevention and detection?” were highly successful. These two reports were found to be great resources for black men, health-care providers, health educators, researchers and the general public. We plan to generate a community report for this study to be distributed during the next TAFF health programme activities in Abeokuta.

Step 12: Manuscript preparation and research translation

This CaPTC project would not have been successfully implemented without partnership with the community, so our community partners will be included as coauthors in the scientific literature from the project such as journal or newspaper articles, presentations and reports.

6. Community engagement from an African perspective: the Khayelitsha case study in South Africa

In 1995, the Khayelitsha Cervical Cancer Screening Project (KCCSP) commenced as a collaboration involving the Department of Obstetrics and Gynaecology of the University of Cape Town, the departments of pathology and epidemiology of Columbia University and the community of Khayelitsha. This project was funded via the Gates Foundation from its inception until 2006, through the Alliance for Cervical Cancer Prevention. Our specific partner was EngenderHealth, a New York based non-profit organization that had worked extensively in reproductive health in developing countries. The project aimed to find methods for preventing cervical cancer in resource-limited settings typical of Africa. It was motivated by the fact that cervical cancer was, and remains, the commonest cancer among women in Africa, affecting at least 80 000 women per year and killing approximately 60 000 yearly, or 78% of women diagnosed with the disease (37). This is entirely due to the lack of access to screening and diagnostic and therapeutic interventions. The Khayelitsha project wanted to test alternatives to cytology, which is effective in reducing the incidence of and mortality from cervical cancer in well-funded, strong health-care systems but had proved too complex to initiate or sustain by poor countries.

The project was timed to be initiated one year after South Africa was liberated from apartheid and the first ever democratic election had been held that saw Nelson Mandela become the country's and the ruling African National Congress president. While there was great euphoria in the country at the time, there was also a great deal of distrust, woundedness and suspicion, and this included in scientific interventions in community-based projects. There was a poorly documented history of scientists "using" communities for research purposes and pulling out of the community after gathering the information, leaving nothing of value behind. The communities were seen as research tools or subjects, and their rights, involvement and needs were either ignored altogether or regarded as secondary to the intentions or needs of the researchers. This, of course, is a generalization, but when the cancer study started in Khayelitsha, we encountered a great deal of resistance. Before our project, a similar project had performed a study that compared visual inspection methods for detection of cervical cancer precursors with cytology. The study had been well conducted and well received by the community; however, once funding ended, the infrastructure established by the researchers was removed along with the service that was provided. The study had used a specially adapted caravan for screening and treatment of lesions. The now relatively sensitized community of women no longer had access to screening for cervical cancer, and the state health-care institutions could not provide this service since they had not yet developed an effective screening programme for the disease.

KCCSP took over from where the old project had stopped but with a completely new protocol. We very quickly realized, however, that we needed to amend the poor image of researchers in the community associated the older study as well as build a new relationship. It was clear to us that we had to fully engage with the community to ensure their participation and that the study design would be acceptable, understandable and meaningful. We needed to listen to the women and their community and to ensure that we created a structure that would be sustainable and deliver on its promises.



Khayelitsha settlement outside Cape Town.

Khayelitsha is a periurban settlement about 20km outside the centre of Cape Town. In 1995 Khayelitsha consisted almost entirely of shacks and informal settlements without electricity or other services such as proper sanitation, indoor water and refuse removal. The community was entirely black and poor with an unemployment rate estimated at 60%. The settlement was characterized by high rates of poverty, crime, violence against women and children and a very high burden of poverty-related health concerns such as tuberculosis, malnutrition, and maternal and neonatal morbidity and mortality. In addition, AIDS was rampant. Some of this has changed over the 18 years that the KCCSP has worked in the area. For instance, some areas now have brick houses and all amenities, but about 30% of the population still lives in shacks. Most residents now have access to sanitation, running water and electricity. New primary care clinics have been built and others upgraded with the much improved, albeit still problematic, health care system. Roads have been paved and new schools and community amenities such as swimming schools, shopping malls, train lines and bus stations have been built.



Cervical cancer screening area at a primary health clinic in Khayelitsha

In 1995 our team focused on two aspects of our proposed work. The first aspect was the development of the research protocol. We aimed to recruit 3000 previously unscreened women aged 35–65 years and to compare the test performance of four screening tests: cytology, visual inspection of the cervix with acetic acid, HPV DNA testing and cervicography, which involved taking a photograph of the cervix with a specially adapted camera after the application of acetic acid. The photographs were developed and read by experts in the USA. All women with any abnormal test were referred for colposcopy and treatment, if appropriate. All procedures were performed in the adapted caravan used by our predecessors, which was parked outside one of the primary care clinics in Khayelitsha.

The second aspect of our work was to build, repair and initiate new relationships with the community. We wanted to share the protocol with them and to earn their trust and support. We began this process by engaging all relevant stakeholders, including:

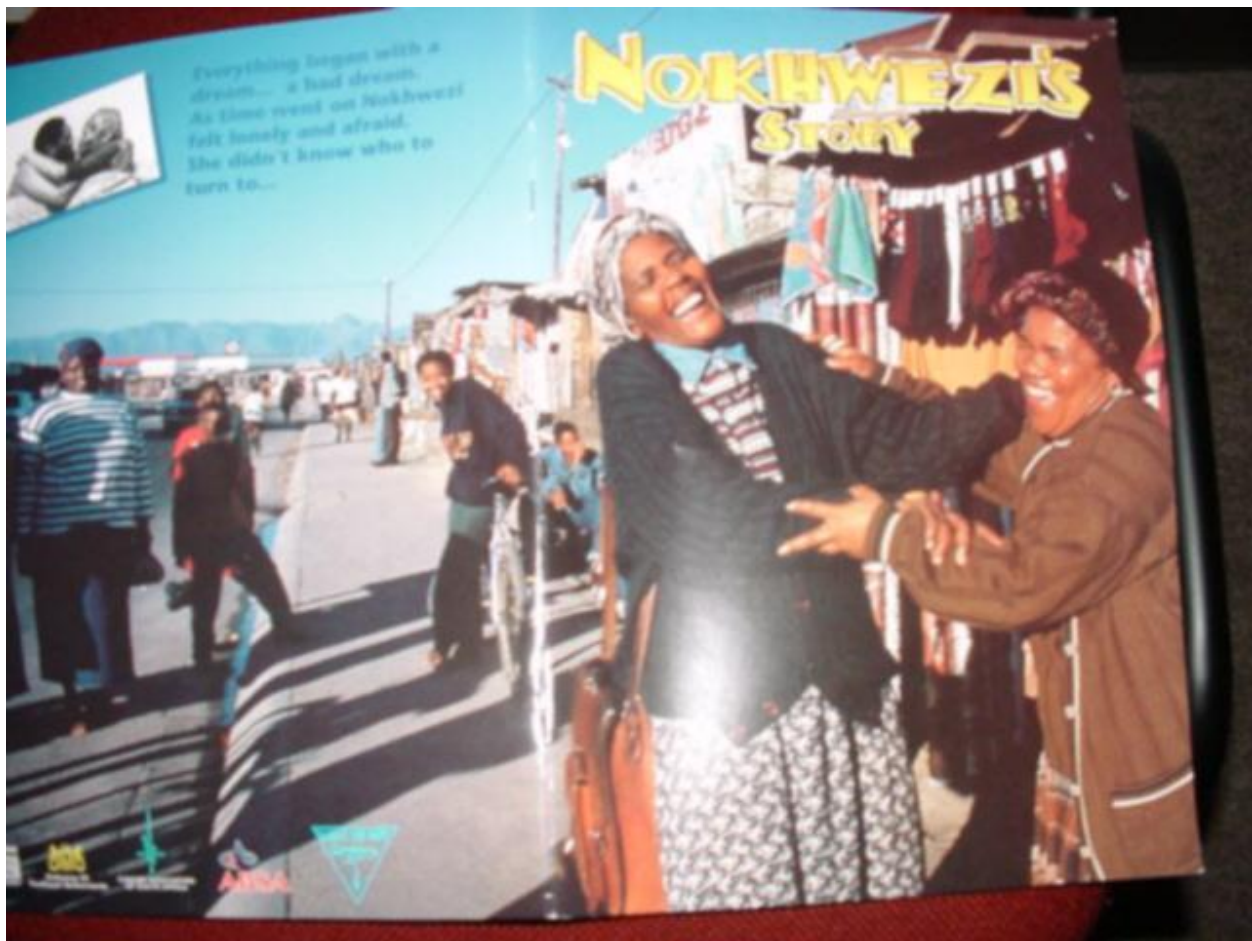
- (a) the local primary health-care system and the local health authorities;
- (b) the Traditional Healer’s Association;
- (c) local political leaders;
- (d) leaders of the newly formed community health forums;
- (e) faith-based organizations and churches;
- (f) NGOs working in reproductive health;
- (g) women’s associations;
- (h) school boards.

This process took six months of regular meetings in which we explained the rationale for the study, the preventability of cervical cancer, our research methods and our plans for sustainability. We were encouraged by the reception from all the groups, who appreciated the fact that we were interested in their opinions and their approval. We also organized a series of “mass meetings” in collaboration with local churches, and as principal investigator, I spoke to groups of up to 100 men and women about cervical cancer on four occasions. These meetings were well attended and many questions were asked and myths about cancer dispelled.

After six months we believed we had achieved our goals of gaining community acceptance and approval and we initiated the study. It took us just under two years to recruit the first 3000 women. During this time we held six monthly mass meetings to communicate results as they were coming in. Besides the mass meetings, we also recruited women from shops, train stations and the streets of Khayelitsha to participate in a series of workshops to design appropriate and meaningful health education materials. This process was pivotal to the design of our health materials and led to the making of a film called “Nokhwezi’s story”, which we converted into a photocomic book and a radio play. The story is about a woman who dies from cervical cancer and her very distressed friend, who hears that you can get tested at the clinic to prevent cancer but is afraid to go to the clinic. Her fear is associated with a number of concerns related to the poor quality of health care services, but is centred around the objection of her husband and in-laws who do not approve of western medicine. Eventually the local traditional healer is consulted and, as it turns out, she herself had had a Pap smear and had been treated for an abnormality. But she still gives the woman traditional medicine. The woman finally gets a Pap smear. The film gives equal value to modern health approaches and cultural imperatives.

We tested the impact of the photocomic and the radio play in a randomized trial in 2004⁽³⁸⁾ in which we recruited 658 women from the community aged 35–65 years. The main outcome measure was self-reported cervical screening uptake six months after the distribution of the photocomic and the running of the radio play. We found that the photocomic was much less effective than the radio play at inducing women to go for screening, although only about 20% of the women who heard the play went for screening compared with 4% who had not heard it. What we learned from this was that health-care messages need to be carefully crafted and tested for effectiveness. We attributed the lack of interest in the photocomic to the relatively low level of literacy in the community. Only 30% of the women had some high school education.

As the project developed, we added HIV testing to the protocol. This required extensive communication with the community, as HIV was highly stigmatized at that time. The community did not give us the approval for HIV testing at first. Because we considered HIV testing so important to our study, we came up with a system of anonymous reporting of HIV test results in which only an independent statistician would be able to link a HIV result to a specific study number, which would be de-identified in terms of name and other attributes. Only when we could assure the community that the results were completely confidential, that the investigators also could not access the results and that women could choose to receive or not to receive their results did we get the community approval to proceed. It was only after this extensive negotiation with the community that we submitted our research protocol to the research ethics committee, who approved it. Our approach is a good example of how a community can impact the research design and how respecting the view of the community can be highly beneficial to both the community and the research.



Khayelitsha Cervical Cancer Screening Project: Nokhwezi's Story

We screened another 3000 women, this time using a new HPV DNA test and adding anonymous HIV testing. During this part of the study we worked extensively with the community on how to counsel on HIV and how to involve the men and to gain their support. We worked with a well-known African playwright to create a theatrical drama addressing reproductive health issues and with a focus on communication between men and women and prevention of HIV and cervical cancer. The play, entitled "Diaries of my womanhood", told stories of the lives of men and women living in Khayelitsha. The drama played at many events in Khayelitsha, all over Cape Town Province and in the mainstream theatres in Cape Town. It was a significant success and it gave our recruitment efforts a big boost.

During the study we conceived the idea of running health festival days. These days were designed to create a festival atmosphere around a diverse range of health issues. We set up stalls, hired halls, brought in street food vendors and invited colleagues working in other health areas including children and immunization, nutrition, HIV, adolescent health, breast health and cervical cancer prevention. We showed our Nokhwezi's story film and had games with prizes, singing, dancing and talks. We continue to hold these festivals every six months.

One of our observations was the high level of stigma associated with the genital tract among women in our study. The genital area was generally considered unclean, unattractive and of concern only for men. This was a significant barrier in preparing women for and undertaking examination of the genital tract. Once again we embarked on a series of workshops, inviting women living in Khayelitsha to join if they so chose. We used the services of a medical anthropologist, who in turn engaged a female praise singer. These workshops were

highly instructive and transformational. The genital tract was renamed “the sacred pathway” and its significant role was highlighted, particularly by the words of one woman: “Even Nelson Mandela was born through the vagina”. The praise singer created this poem:

*Vagina is the flower of the nation
It looks like a strawberry
It looks like a beautiful girl
It is reddish in colour and looks like an apricot
It looks like a lily
The womb is the cave of life which produces life
The flexible passageway opens like a curtain
Acts like a channel to produce life
Is this a secret the way we give birth?
Because kings and queens, presidents of parliament,
graduates come from the cave of life*

This became the signature poem of KCCSP and was extremely well received by all stakeholders in the community.

We realized that the quality of the primary health care provided to the women was poor and a factor in why women were not being screened for cancer. We conducted another randomized trial, interviewing over 600 women to understand their issues. One third of the women reported “womb-related problems” in the previous 12 months, two thirds of whom had sought help. Over half of the women reported “vagina-related problems”.⁽³⁹⁾ We initiated an education programme involving monthly lectures on relevant topics for health-care providers, who were doctors and nurses employed by the public sector. It became evident too that very few women in our study were “asymptomatic”, and when we systematically analysed this information we found out that 30% of the women required referral for health problems not related to the cervix, including diabetes, hypertension and other noncommunicable diseases. The most common reason for referral was infertility, a major source of morbidity among poor women. While we continued with screening, we realized the importance of providing women with a holistic service, so we have continued to include reproductive and other services in all our various projects.

The largest study undertaken by KCCSP involved 7000 women. Women were randomly assigned to various “screen and treat” strategies.⁽⁴⁰⁾ The community gave permission for HIV testing but we did not include in the study women who refused to be tested for HIV. We embarked on a major educational campaign and each woman was given extensive pre- and post-HIV testing counselling, which proved to be a very valuable model. Again we engaged the community in designing the educational materials through workshops. Their input was invaluable.

KCCSP still continues its cervical cancer prevention work. We recently completed a randomized trial on HPV vaccination of HIV-positive women aged 18–25 years. We continue to provide HIV screening to women who request it and education to health-care providers and are closely involved with boosting and supporting public sector screening activity. KCCSP is a key adviser to the Minister of National Health on Cervical Cancer Prevention and has been instrumental in designing the current policy for South Africa.

It is clear that CBPR is not only necessary but should be mandatory. The tenets of good clinical practice, which include respect for persons, beneficence and justice,⁽⁴¹⁾ cannot be guaranteed without full engagement with the communities in which research is conducted. There are far too many recorded instances of research misconduct historically, particularly in Africa, where patients are poorly educated and informed about their human rights, where health-care systems are fragile and inadequate, making access to research interventions more appealing, and where regulatory bodies are insufficient, ineffective or corrupt. Community engagement not only empowers our patients, it informs and strengthens the validity of our research protocols.

7. Conclusion

According to the African Organization for Research and Training in Cancer (AORTIC), “Approaches to minimize the burden of cancer in sub-Saharan Africa in the past few years have had little success because of low awareness of the cancer burden and a poor understanding of the potential for cancer prevention”⁽⁴²⁾ To successfully address the disproportionate burden of cancer in Africa, it is important that the communities affected by the disease be engaged and work closely with cancer researchers. Acting “on the community” is no longer an option for researchers as this approach has failed to improve community health or mitigate public-health problems. The only option is for researchers to act in partnership “with the community”.

It is important to note that CEnR cannot be regarded as a cookbook approach to research. It is an active process of developing a relationship with the community of interest. As with any relationship, it takes time, patience, trust and commitment, and as with any covenant relationship, it can be quite rewarding for all the parties involved. As illustrated by the African proverb, “When spider webs unite, they can tie up a lion”, when scientists and community leaders unite, they can conquer cancer in Africa.

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Chapter 7

Biosampling and biobanking

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Chapter outline

1. Background and introduction
2. Collection and processing of biospecimens
3. Biospecimen storage facilities
4. Information technology in biobanking
5. Regulation in biobanking

1. Background and introduction

The global total of new cancer cases is projected to increase by 60% to 21 million annually by 2030, with an estimated 13.1 million deaths from cancer yearly. About half of these cancer deaths will occur in low-income countries and more than 80% of these in African countries.^(1,2) It is thus crucial that appropriate interventions be implemented to confront this situation. Biobanks play an important role in the study of cancer etiology and identification of new potential diagnostic markers, and are central to the development of personalized drug treatment and translational research (3–5). Investments in biobank infrastructure will enable scientific progress, on which effective cancer control measures depend.

The aim of this chapter is to provide information on the collection, processing and storage of biospecimens and the management of biobanks as a valuable tool for cancer research in Africa. A biobank, defined as a facility for the long-term storage of biospecimens, is a key resource providing for access to high-quality human biospecimens. The combination of infrastructure, facilities and resources is referred to as a biological resource centre (BRC). Tumour banks are BRCs; they have been defined by the Organisation for Economic Cooperation and Development (OECD) as service providers and repositories of living cells, of genomes of organisms, of cells and tissues, and of information relating to these materials.

Technological advances in molecular biology and genetics have greatly enhanced our ability to investigate the interactions among genetics, the environment, lifestyle and health. Biobanks consisting of biospecimens from clinical and epidemiological studies provide the opportunity to more effectively study disease causation and prognosis. Nowadays, analytical methods have developed to a level where they can be applied to large numbers of biospecimens, so biobanks play a cornerstone role in genetic and molecular epidemiology studies.

The management of BRCs requires comprehensive quality management systems with appropriate controls. These are necessary to ensure that biospecimens collected for clinical or research purposes are of consistently high quality and are appropriate for the intended analyses and study goals.⁽⁶⁾ Despite advances in biobanking activities in high-income countries, populations in Africa are underrepresented in sharing of these resources owing to their economic constraints and related issues. This means that studies are conducted without adequate representation of the populations that are mostly affected by the life-threatening diseases. Many research studies have been conducted in Africa, but apart from the biobanks created in HIV treatment facilities for HIV research involving large numbers of individuals,^(7,8) no other research study has found it necessary to establish a biobank, mainly because the sample sizes for many non-HIV studies are small, and the studies very rarely collect and store frozen plasma or DNA for further biochemical and genetic studies. When such biospecimens are collected, their collection and storage are not planned or organized in any

systematic way. In the absence of biobank studies in sub-Saharan Africa, Campbell and Rudan⁽⁹⁾ conducted a systematic review of birth cohort studies to assess the resources available to support genetic epidemiological studies. Their results showed that less than 40% of the 28 studies included in the review collected biological material and less than 20% collected and stored DNA.

In the absence of adequate funding for and awareness of the benefits of biobanks, the challenge for Africa to establish and maintain suitable infrastructure consisting of biospecimens cold storage facilities, databases, reliable electricity supply to maintain the equipment, and quality assurance tools is no mean feat. Nevertheless, the first national DNA bank in Africa was established in 2000 in the Gambia as one of 14 such collection sites created by the Medical Research Council to study the genetics of the complicated diseases of malaria, HIV/AIDS and tuberculosis.⁽¹⁰⁾ The facility in the Gambia has expanded over the years and has continued to support research activities.

Although there is a plethora of guidelines and protocols for biospecimen processing,⁽⁶⁾ the tools are not easily accessible in Africa, which makes it difficult to adhere to best practice principles defined in international protocols. It is important therefore that alternative and cheaper options of evidence-based protocols be developed for Africa.

The aim of this chapter is to promote good practices in human sample biobanking in Africa to facilitate the appropriate collection of samples for the development of local cancer research and international collaboration. Underpinning all this is the need to have well-trained staff to operate the facilities and manage the different processes involved in providing high-quality biospecimens, to develop appropriate technologies applicable to local settings, to handle the day-to-day activities, and to deal with issues relating to sample access and patient confidentiality. Information is provided on requirements for cold storage facilities and on the development and management of databases. The emphasis here is on presenting the basic requirements for BRCs or biobanks to store and maintain high-quality biospecimens and on providing guidelines to ensure that research is conducted with integrity and in adherence to the highest ethical standards according to international regulations and rules governing ethical, legal and social issues (ELSI).

This chapter provides information on the value of studies on pre-analytical variability of biospecimens—which are crucial in ensuring the integrity of downstream analytical results⁽¹¹⁾—and how biospecimen science research can offer the opportunity to develop and validate appropriate technology and tools for Africa. In particular, research to help identify quality-control biomarkers for assessing the quality of samples before they are included in expensive research platforms would reduce costs and free up the limited funds to be spent elsewhere.

2. Collection and processing of biospecimens

Collection, annotation and use of human biospecimens are essential activities in cancer research. Biobanking is also becoming a critical process in allowing patients access to molecular-based diagnosis and prognosis. Tumour banks need to comply with strict technical requirements. The definition of a tumour bank includes not only the infrastructure for collecting, archiving and storing biospecimens and data but also the procedures and services for informing patients; obtaining consent; collecting and processing specimens for secure, long-term storage; appropriately accessing and retrieving specimens for analysis; and processing specimens for preparation of molecular derivatives such as DNA, RNA and proteins for quality control and for distribution to cancer researchers.

Two types of methods must be distinguished: (a) processing methods, which include different types of biospecimen handling, such as snap-freezing, paraffin embedding, plasma and buffy coat preparation, nucleic acid extraction, and establishment of cell lines, and (b) quality control methods, which enable characterization of the biospecimens, such as the minimal sample characterization data set.

Biospecimen processing

The types of samples collected during clinical practice include bodily secretions, tissue and fluids. Using samples left over from clinical diagnostic procedures for biobanking purposes is generally not an optimal practice. Instead, dedicated specimens for biobanking and research should be collected at the same time as diagnostic specimens but in separate containers and processed through separate standardized workflows. The critical steps in each processing method should be acknowledged and controlled.

The biospecimen processing method may depend on the anticipated end use. It is difficult for a biobank to anticipate all the different future uses for the samples, therefore, the most stringent processing requirements should be followed by the biobank to maximize the lifespan and potential uses of the samples. Since for all sample types the impact of freezing and thawing on future target molecules is unknown, the number of freeze-thaw cycles should be kept at a minimum. For that reason, small volumes of aliquots should be prepared before cryostorage, of about $\leq 200\mu\text{l}$ for serum and plasma, and $\leq 0.5\text{ cm}^3$ for frozen tissue.

Prospective biospecimen collections generally have the most added value. Longitudinal follow-up of patients allows the establishment of causal links instead of simple associations between observed clinical end-points and candidate surrogate biomarkers. Improving such studies requires coding of samples instead of irreversible anonymization and, most importantly, adequate human resources such as clinical research nurses for follow-up. Furthermore, inclusion of coded family links adds value to the collection.

For biological fluids or solid tissue samples intended for immunological, molecular biology or proteomic analyses, critical *in vitro* pre-analytical details should be accurately recorded. For the fluids, this information includes the type of primary collection tube, pre-centrifugation time delay and temperature, centrifugation conditions, post-centrifugation time delay and temperature, and long-term storage duration and temperature. For solid tissues, this information includes warm and cold ischemia times, type and duration of fixation, and long-term storage duration and conditions.⁽¹²⁾ Refrigeration and short processing delays are crucial, especially for urine collected without preservatives. If the samples are intended for proteomic downstream applications, high-speed centrifugation should be used, ensuring removal of white blood cells and platelets. The “as soon as possible” recommendation for pre-analytical processing is not precise enough. A simple way of tracking pre-analytical information is through the Standard PREanalytical Code (SPREC), a simple seven-element code that enables all pre-analytical information to be captured for the different types of specimens.⁽¹³⁾ This information can be added as a searchable data element in the biobank database. Finally, if metabolomic applications are anticipated, *in vivo* pre-analytical data—including the time of day when the blood or urine samples were collected, medications taken by the patient and food intake—should also be recorded in appropriate databases. Standard operating procedures (SOPs) for different types of biospecimens being collected and processed in tumour banks can be found on the web sites of the International Society for Biological and Environmental Repositories (ISBER) Best Practices for Repositories (www.isber.org/bp), the Canadian Tumour Repository Network (CTRNet) (<http://www.ctrnet.ca/operating-procedures>), the Biorepositories and Biospecimen Research Branch (BBRB) (<http://biospecimens.cancer.gov/rsources/sops/library.asp>), and the International Agency for Research on Cancer (IARC) (<http://www.iarc.fr/en/publications/pdfs-online/wrk/wrk2/index.php>), as well as from Molecular Medicine Ireland.⁽¹⁴⁾

Other types of samples that can be collected include human DNA for genetic susceptibility testing, human RNA from peripheral blood for gene expression signatures such as prognostic or predictive biomarkers of treatment outcome, and peripheral blood mononuclear cells for cell sorting and cell immunophenotyping. Coordination of project-specific prospective collections is also possible, for example collecting urine with protease inhibitors or plasma for peptidomics analyses. As a general rule, tubes and kits for collecting and processing biospecimens should be obtained from commercial suppliers. The advantage of using such devices is that they have already undergone significant validation by the suppliers. However, since this validation

often focuses on specific quality attributes or specific molecules in the sample, the tumour bank still has to validate the collection or processing device for other target molecules when these become known.

All human specimens regardless of the known disease state of the patient should be treated as potential biohazards. This is because the patient may have a contagious disease that has not yet been diagnosed. Appropriate measures should be taken to protect laboratory workers who handle specimens and to prevent others from being exposed to the specimens during transportation. This is a good laboratory practice. The most commonly collected and processed biospecimens include blood, urine and tissue.

Blood specimens

Whole blood samples. Whole blood does not require any special processing for storage and can be stored at -80 °C or room temperature or as dried blood spots on filter paper. Storage of whole blood samples is necessary if the end use is DNA analysis. DNA is a very stable molecule that is robust to a range of storage conditions. Whole-genome sequencing requires higher-quality DNA samples than do single-target PCR assays. However, whole-genome amplification can be performed to obtain large quantities of DNA from minute amounts.⁽¹⁵⁾ When anticoagulated blood is centrifuged it separates into the red blood cell (RBC) fraction and the buffy coat layer containing white blood cells (WBC), platelets and plasma. When coagulated blood is centrifuged it separates into the clot (RBC, WBC and platelets) and serum.

Dried blood spots. In the African context, storage of whole blood as dried blood spots (DBS) makes sense, as this avoids technical problems related to cryostorage and logistical arrangements. DBS can be used effectively for DNA sequence analysis for up to three decades of storage⁽¹⁶⁾ and for cytokine measurements for up to two decades of storage at -20°C.⁽¹⁷⁾ DBS testing is a powerful tool for screening programmes and large population-based surveys, for detection of biomarkers such as hepatocellular carcinoma⁽¹⁸⁾ and for large-scale testing for HIV infection.⁽¹⁹⁾ Special attention should be paid to card selection, collection method and storage.

Plasma is the liquid fraction of anticoagulated blood. Different anticoagulants may be used, such as ethylenediamine tetra-acetic acid (EDTA), heparin and acid citrate dextrose (ACD). The end use of the blood influences the choice of the anticoagulant. ACD is the preferred anticoagulant when lymphocytes from the cellular fraction of the blood are to be used to establish lymphoblastoid cell lines, but citrate interferes with future metabolomic analyses in the plasma. Heparin may inhibit nucleic acid amplification and future molecular biology analyses in the nucleic acid samples obtained either from the cellular blood fraction or plasma itself (circulating nucleic acids). Therefore, EDTA is preferred as it allows proteomic, genomic and metabolomic analyses to be performed in the future.⁽²⁰⁾ Platelet-poor plasma can be obtained after blood centrifugation at high speeds (>3000 g) and is more suitable for proteomic analyses because it allows less interference by circulating platelets and other coagulation factors.⁽²¹⁾ Time delays and temperatures to which the blood is exposed between collection and centrifugation and between centrifugation and plasma storage must be carefully documented.⁽¹³⁾ There is no consensus about time delays and temperatures that the collected blood can tolerate, but it has been shown that pre-centrifugation delays of up to eight hours at room temperature do not significantly alter proteomic profiles.⁽²²⁾ For longer pre-centrifugation delays, storage at 4 °C is preferred. For specific target analytes in the context of cancer research projects, validation should be performed to deal with the impact of the time delays.⁽²³⁾ Storage of plasma should be at -80°C, which is the temperature that has been found to ensure stability of the vast majority of molecules examined to date.⁽²⁴⁾ Validation has not yet been performed of lyophilized plasma and its storage at different temperatures, including room temperature.

Serum is the liquid fraction of clotted blood. Preparing and storing serum instead of plasma offers two advantages for a tumour bank: (a) serum does not contain platelets and coagulation factors and therefore it allows proteomic analysis of a greater number of proteins, including those that cannot be identified in plasma because they are bound to plasma coagulation factors,⁽²²⁾ and (b) the absence of additives in serum ensures

there will be no interference from such elements in downstream spectrometric analyses.⁽²⁰⁾ As with plasma, it is very important to document for serum the time delays and storage temperatures from blood collection to centrifugation (clotting time) and from centrifugation to storage. The same considerations for storage temperatures are observed for serum as for plasma. For both types of samples, the inflammatory status of the donor is an important confounder if the anticipated use is proteomic analysis; therefore normalization of the samples relative to the inflammatory status may need to be performed.

Peripheral blood mononuclear cells (PBMCs) include lymphocytes and monocytes. These cells can be isolated from the buffy coat layer of centrifuged anticoagulated blood through Ficoll gradient centrifugation. PBMCs should either be stored at -80°C, preferably in lysis buffer if they are intended for gene expression analyses, or cryopreserved as viable cells in liquid nitrogen (LN2) using the cryopreservation medium dimethyl sulfoxide (DMSO) if they are for future cell sorting, cell immunophenotyping or immortalization and establishment of lymphoblastoid cell lines for an unlimited source of DNA. Although preparation of PBMCs from anticoagulated blood for gene expression analysis is possible, if transcriptional analysis is the anticipated downstream application, collection and processing of blood in one of the commercially available RNA-stabilization blood collection tubes, such as PAXgene RNA tubes or Tempus tubes, is preferred, because of the uncertainty associated with the influence of pre-analytical conditions on gene-expression profiles (25). For viable lymphocyte isolation, ACD blood collection tubes are preferable, and the delay between blood collection and processing can be three to four days at room temperature. If Ficoll gradient centrifugation is not possible, whole blood can be cryopreserved and used for viable lymphocyte processing or analysis in the future. Keeping whole blood at 4°C for several hours before progressive-rate freezing in DMSO allows recovery of viable lymphocytes.⁽²⁶⁾

Urine specimens

Urine contains DNA, RNA, proteins and metabolites, and since it is easy to collect, it can be collected and stored for analysis of all of these molecules. However, because urine composition lacks tight homeostasis and depends on disease status, the time of the day it was collected and donor hydration status, it needs to be normalized for proteomic analyses. For proteomic or metabolomic analysis, urine is centrifuged and the supernatant is aliquoted and stored at -80°C. Centrifugation is necessary to avoid interference by cell components. For DNA or RNA analysis, the pellet is stored preferably in a nucleic acid stabilization solution such as a cell protect reagent. Filtration of the supernatant must also be performed for proteomic analysis,⁽²⁷⁾ but this step can occur after thawing and immediately before analysis. Collecting midstream, first or second morning urine is preferred, and in all cases, collection time and delays should be documented.⁽¹³⁾ Refrigeration is preferred to avoid bacterial proliferation. Different urine preservatives such as boric acid or sodium azide may also be used to prolong processing delays if the urine is stored at either room temperature or 4°C.⁽²⁸⁾ If metabolomic analysis is the anticipated application, use of preservatives may influence spectrometric analyses and filtration will not prevent enzymatic reactions, leading to metabolomic changes. In this case, maintaining the urine at 4 °C or freezing it within one hour of collection is recommended.⁽²⁰⁾ EDTA also has been reported as a DNA stabilizer in urine, although its efficiency has not been reproducible in Africa.⁽²⁹⁾ Useful information on urine collection and processing has recently been published.⁽²⁷⁾

Tissue specimens

Dissection. A general rule in tumour banking is that tissue sampling locations and tissue amounts for research must not interfere with routine diagnostics and staging. Once the specimen has been weighed, measured and photographed by the pathologist, areas with normal and abnormal tissue are sampled by gross examination. Several 6–8 mm dermatome core biopsies may be performed. This procedure allows easy visual localization of the sampling spots. Alternatively, an 18-gauge biopsy gun can be used to obtain small cores of tissue. Ensuring sterility and avoiding cross-contamination during dissection are critical factors for downstream

molecular biology analyses. Disposable absorbent pads can be used to create a clean field, and sterile blades, gloves and disposable knives should be used.

Freezing. Tissue sections are immersed into either an isopentane bath previously cooled in LN₂ or directly into an LN₂ dewar. Tissue should be 0.5cm³ or thinner for quick freezing. A minimum of two to three minutes is needed for complete freezing. Frozen samples are then transported to the tumour bank in dry ice. An optimal cutting temperature (OCT) compound can be used to embed and freeze the tissue, to allow for future cryosections and morphological examination, or molecular extractions and analyses. Frozen tissue specimens should never be allowed to thaw, which would not only destroy the sample's morphology but also cause severe RNA degradation.

Stabilization and fixation. Different types of tissue fixatives are available. The standard fixative for preserving morphology is 10% neutral buffered formalin (NBF), but it causes molecular cross-linking and undermines the quality of DNA, RNA and proteins that can be extracted from a formalin-fixed, paraffin-embedded (FFPE) block. For best fixation, samples should not exceed 0.5cm³ in size. Samples should be fixed in 10 volumes or more of NBF. Routine fixation should be for approximately 12 hours overnight. After fixation, the tissue specimen is removed and placed in 70% ethanol for shipping or further processing in paraffin. PAXgene tissue fixative (Qiagen) allows for morphology preservation and at the same time ensures high quality of DNA, RNA and proteins. The only drawback seems to be the eventual necessity of revalidating the immunohistochemical (IHC) assay parameters for PAXgene-fixed, paraffin-embedded (PFPE) tissue. Alcohol-based fixatives also are available, including Omnifix and other proprietary fixatives. A section should always be made from fixed tissue for immediate histopathological quality control. Tissue stabilizers exist that allow stabilization of molecules but do not preserve tissue morphology. RNALater (Ambion) is an aqueous non-toxic tissue storage reagent that rapidly permeates tissue and stabilizes all nucleic acids. AllProtect (Qiagen) reagent allows stabilization and subsequent extraction of both nucleic acids and proteins. These stabilizers eliminate the need to process tissue samples immediately or to freeze them. Finally, heat stabilization under vacuum (Denator) conditions with the subsequent storage of the heat-stabilized tissue at -80°C has been shown to effectively preserve tissue phosphoproteome, although it does not allow for morphology or nucleic acid analysis.⁽³⁰⁾

Laser capture microdissection (LCM) is a technique that allows isolation of pure cell populations from heterogeneous tissue sections through direct visualization of the cells. Automated LCM platforms combine a graphical-user interface and annotation software for visualization of the tissue of interest and robotically controlled microdissection. RNA degradation may be minimized by limiting the duration of the staining procedures, while protein degradation may be minimized by adding propidium iodide (PI) to the staining reagents or limiting the microdissection session to one hour. Microdissected cells for protein analysis may be stored at -80°C before extraction, while for DNA analysis they may be stored desiccated at room temperature for up to one week before extraction. For RNA analysis the samples should not be stored to begin with, but RNA extraction should be performed immediately after microdissection and then the RNA samples stored at -80°C.

Tissue microarrays (TMAs) are slides that contain several minute specimens from different FFPE blocks. They are prepared by transferring paraffin tissue cores from many "donor" blocks to one "recipient" block. Each slide cut from this recipient block is called a TMA slide. TMAs are ideal for efficient screening of prospective biomarkers by IHC, fluorescence in situ hybridization (FISH) and RNA in situ hybridization methods. "Frozen" TMAs may also be prepared using frozen donor tissues embedded in the OCT compound. These samples are then arrayed into a recipient OCT block. This allows high throughput evaluation of frozen tissue with corresponding visualization of tissue morphology. To preserve antigenicity, a fresh section should be cut at the time of evaluation or the TMA sections should be stored in a vacuum, in a nitrogen gas environment or at -80°C, to avoid antigen degradation due to oxidation. TMAs should have positive controls for the anticipated IHC assays.

Biospecimen quality control

Quality control (QC) procedures are important to ensure data and sample quality. For data, this includes clinical data accuracy, whereas for biospecimens it includes assays on the authenticity, integrity and identity of the samples.⁽¹²⁾ Biospecimen QC is required to ensure accurate sample characterization and classification and to avoid introducing bias in downstream research due to intrinsic heterogeneity of the sample. This bias was shown in a specific African breast cancer classification study.⁽³¹⁾ The type of QC depends on the intended end use of the sample. For example, samples to be used as reference samples in commercialized diagnostic kits must undergo mandatory testing for HIV, hepatitis B virus (HBC) and HCV. A central QC laboratory can undertake this testing, and the critical steps in each QC assay should be acknowledged and controlled by the laboratory. Accurate characterization of the samples supplied by a tumour bank focuses on both the authenticity and the integrity of the biomaterial. As an example, when a biobank supplies a serum sample from a patient with “primary melanoma”, the sample should indeed represent a primary melanoma status (authenticity) and its status should not have been compromised by any type of pre-analytical bias (integrity).

Authenticity. Phenotypic QC methods generally used for authentication of cancer tissue specimens involve histopathological assessment. The histopathological validation of tissue samples (fixed and/or frozen sections) test, which needs to be performed by a trained pathologist, aims to confirm the tissue type, that is if it is from a tumour or normal tissue, and the basic histopathological diagnosis and classification, based on standard hematoxylin-eosin staining. The test includes assessment of cellular composition, which is of critical importance in any downstream molecular analysis. A highly heterogeneous cellular composition makes any molecular analysis irrelevant, and the minimum proportion of tumour is generally set at 70%. The standard histological control also includes assessment of specimen morphological degradation. Histopathological testing allows identification and marking of the block areas that are the most suitable for TMA cores. There may be special advantages in developing and implementing histopathological QC by telepathology in Africa. Static telepathology, or microscopic photographs, is based on offline imaging without interaction between operators. The software Windows Live Messenger and Skype can be used for image transmission at very low cost. Virtual microscopy and dynamic telepathology allow production of “virtual slides” using navigation tools on the Internet.

Integrity. Very few data are available on the value of QC tools in assessing collection procedures and shipping and storage conditions. However, homogeneity in these steps is key for quality multicentre research studies. For effective QC of retrospective collections, tumour bank managers can proceed in several ways. QC can be performed on every specimen received at the biobank. In some instances this is highly recommended and cost-effective, for example haemocytometry for all blood samples. In other instances generalized quality control for samples received at the biobank is not cost-effective, such as for specimens for DNA extraction and analysis. In that case, QC may be performed before distribution of samples to researchers, for example for verification of DNA concentration, purity or Taq amplifiability, provided that such the QC does not destroy the sample. Retrospective QC is always an option and two alternatives are available: testing either a randomly selected percentage of the collected specimens or samples considered to have undergone the most “inconsistent” processing. The first approach allows comparisons of collection sites, while the second allows targeted assessment of “highest risk” samples.

Certain QC assays may be performed by the biobank, the end-user who finally receives the samples or a subcontracting laboratory, such as the following: QC tests allowing more accurate characterization and ensuring more efficient downstream analyses that include but are not limited to (a) C-reactive protein (CRP) measurement in serum to assess the inflammation degree and the corresponding normalization of downstream proteomic analyses, (b) measurement of creatinine and cystatin-C in urine to normalize protein content in view of downstream proteomic analyses, and (c) histopathological evaluation of tissues to normalize the percentage of the tumour.

QC tests for assessment of shipping, processing and storage conditions, including but not limited to (a) serum sCD40L measurement to determine the time the serum samples were exposed to ambient temperatures,⁽³²⁾ (b) haemoglobin measurement in serum or plasma to assess haemolysis that may have occurred during blood sample collection or prolonged pre-centrifugation delays, (c) serum fingerprinting to identify samples,⁽³³⁾ (d) microparticle counting in serum or plasma to assess centrifugation conditions and efficiency, (e) measurement of the platelet activation component to assess platelet activation during sample processing, and (f) molecular QC assessment of tissue integrity by IHC assay, which may cover vimentin, cytokeratins, surface kinases, hypoxia-related molecules and hormone receptors.

DNA QC assays, including DNA quantification and purity analysis by spectrophotometry or fluorometry and gel electrophoresis. PCR assays can assess the degree of DNA cross-linking and the fitness for purpose of DNA in downstream whole-genome amplification (WGA) or array-comparative genomic hybridization (aCGH).⁽³⁴⁾ Possible inhibitors can be detected by the SPUD real-time PCR assay.⁽³⁵⁾

RNA QC assays, including total RNA quantification by spectrophotometry or fluorometry and RNA integrity assessment by RNA integrity number (RIN) measurement. RT-PCR, by amplifying specific cDNA targets (such as GAPDH) using combinations of primers designed to amplify fragments with progressively larger sizes (100 bp, 200 bp, 300 bp, 400 bp), can be used to assess the maximum amplifiable size of RNA. miRNAs molecules, which are increasingly being used in cancer research, can be extracted from any type of biospecimen including tissues, serum and plasma. They are less likely to be degraded compared with other RNA molecules. Real-time RT PCR for generally expressed miRNAs, such as miR16, can be used to determine the presence of the miRNA fraction in an RNA sample.

Plasma and serum QC. Biospecimen research is in progress to identify appropriate QC tools for serum, plasma and urine.^(36,37) Such QC markers may be serum sCD40L to assess the duration of exposure of the sample to room temperature, protein S activity in plasma and matrix metalloproteases in serum or plasma. Serum sCD40L assays are particularly relevant in Africa, where high ambient temperatures are more often observed.

Biospecimen research in Africa

Variability in acquisition, processing and storage of samples may contribute to experimental variability, particularly in high-throughput analyses, and may result in false research conclusions. This is especially true for the most labile bioanalytes like RNA, functional proteins and metabolites. In this respect, biospecimen research is linked to tumour bank biospecimen QC. For both targeted and whole-genome transcriptome or proteome-derived biomarkers, biospecimen research allows assessment of robustness of the biomarker relative to the pre-analytical variations that are expected to occur during sample collection and processing in real conditions.⁽³⁷⁾ For instance, cytokines such as G-CSF, CXCL10, MIF, serpin E and CXCL12 have been shown to decrease in serum with increasing numbers of freeze-thaw cycles,⁽³²⁾ and careful attention is needed in studies targeting cytokines to avoid any pre-analytical bias.

High-quality nucleic acids and adequate antigen preservation can be obtained from formalin-, PAXgene- or ethanol-fixed, paraffin-embedded tissues or from DBS on filter paper. Because these types of biospecimen processing techniques suit the logistical conditions in Africa since they do not need cryostorage, tumour banks in Africa could develop expertise in these approaches of maintaining biospecimen stability and robustness in the context of novel, dried blood, room-temperature technologies, including lyophilization, and in room-temperature storage devices for nucleic acids, or even for whole blood.

Choosing the best collection method

Choosing the right procedures for collecting and storing samples and data is very important, and such decisions need to be carefully considered even before the samples and data are collected. All samples and data used within one experiment must at least fit the purpose of the planned or anticipated experiments and

be of comparable quality. Comparable quality demands that pre-analytical conditions be kept as constant as possible for every sample. Therefore, every sample should be collected in exactly the same way. In addition, the conditions should be the same for all samples during collection and storage procedures. If samples for one experiment need to be collected under certain difficult circumstances, then the collection procedure of choice must be the most feasible under the most difficult circumstances anticipated. However, if using the procedure would result in samples that are not fit for the purpose, then the choice should be to not collect samples under the most difficult conditions or to reject the samples that are not fit for the purpose. Changing the collection or storage procedures while the collection is underway can have consequences for the results from the experiment in which these samples are used and should therefore be carefully considered. Changes implemented during sample collection should be documented in the sample data. The conclusion is that before collection starts, the conditions for collecting and storing the samples and the kind of experiments they will be used for must be largely known. Fit for purpose can be set as a minimum standard for the quality of samples to be collected. But if the collection circumstances pose a limitation for achieving high quality, the resulting samples and data may be used later for more sensitive experiments, making them more valuable scientifically.

For these reasons it is very important to have written SOPs for at least the collection, storage and distribution of samples. In addition, it is essential to ensure that the SOPs are followed and interpreted in the same way during sample collection and storage. Regular audits and QC are needed to check compliance with the SOPs. For example, if tissue is needed for isolation of DNA in combination with histology, FFPE tissues could be used with fixation times of 24 hours if fragmented DNA is allowed. However, when DNA of high quality is needed, other stabilization methods would be needed such as PAXgene tissue fixation.⁽³⁸⁾ In RNA expression experiments, RNA stabilization methods could be preferred, but if RNA expression is combined with histology those methods would not be a good choice. Formalin would result in poor-quality mRNA but reasonable-quality miRNA, and although some proteomics analysis would be possible, unfortunately it would not be for all proteins.⁽³⁹⁾ Snap-freezing would resolve all these difficulties.

All these methods indicate the need for storage facilities. FFPE materials must be stored at room temperature, meaning that in most countries the storage room would need air conditioning to maintain the temperature below 25 °C. Mechanical freezers need clean, cool rooms since they produce a lot of heat. Transportation of samples in warm cars before storage can be detrimental for many methods, and thus cooling is often required during transportation and also for equalizing the pre-analytical phase of all samples in the collection.

The same care should be taken for blood samples. The type of sample; the DNA, RNA or protein of interest and the required sample quality need to be considered. Again, all samples must be of equal or comparable quality, so compliance with respect to clotting time and type of tube is of major importance. The IARC publication *Common minimum technical standards and protocols for biological resource centres dedicated to cancer research* (<http://www.iarc.fr/en/publications/pdfs-online/wrk/wrk2/index.php>) is a source of valuable information.

Quality assurance

Certification of a biobank to international standards such as ISO 9001 (quality management systems—requirements) by an independent body is proof that the biobank is effectively organized and managed. Furthermore, subcontracting testing to laboratories that are themselves accredited to international standards such as ISO 17025 (general requirements for the competence of testing and calibration laboratories) or ISO 15189 (medical laboratories—particular requirements for quality and competence) by a national accreditation body is proof of reliability of the sample characterization processes. Currently, although compliance with these standards is important, it essentially remains voluntary for the biobanks.

3. Biospecimen storage facilities and equipment

Biospecimen storage facilities are the most visible part of biobanks, and storage systems are important factors in maintaining sample quality. The variety of storage systems available for specimen collection increases as technologies advance. Storage equipment should be selected based on the type of specimens to be stored, the anticipated length of storage time for the specimens, the use intended for the specimens, and the resources available for purchasing the equipment (ISBER Best Practices for Repositories; www.isber.org/bp). In selecting equipment, quality issues should be considered, but for a local setting with limited access to tools, the primary considerations should be the available resources, staffing requirements and equipment support and maintenance. For the sample storage equipment, such as freezers, and for infrastructure equipment, such as electrical power and backup systems, LN2 bulk tanks, and transport pipes, compatibility with local conditions and the capacity of the vendor to provide on-site support and maintenance for the time they are used by the biospecimen storage facility should be verified.

Two types of storage systems are described here: ultra- or low-temperature storage systems and ambient-temperature storage systems.

Storage containers

In selecting storage containers for biospecimens, consideration should be given to:

- (a) sample volume;
- (b) necessary cooling and warming rates for both the individual container and the racks, boxes, or goblets;
- (c) potential risk of contamination of the sample or the environment;
- (d) storage temperature and conditions;
- (e) space available for sample storage;
- (f) frequency of access considerations;
- (g) specimen identification requirements;
- (h) specimen preparation and after-storage processing techniques;
- (i) economic aspects.

Containers used in cryogenic temperatures should be rated for these temperatures and should be hermetically sealed for storage in LN2 to avoid penetration of LN2 into the container and consequent risk of contamination and explosion when the container is removed from the freezer. All human specimens should be treated as potential biohazards, and the choice of storage container should integrate minimizing the risk of contamination of laboratory workers who handle the specimens and preventing others from being exposed to the samples in the laboratory or during transportation. This is also a good laboratory practice. Identification labels should be compatible with the storage temperature and medium and should always include eye-readable codes when access to scanners for barcodes, 2D codes or RFID codes cannot be guaranteed by the sample processing institution or end-user.

Liquid nitrogen freezers

Cryogenic storage using LN2 is an effective long-term storage platform because its extreme cold temperatures slow down most chemical and physical reactions that cause specimens to deteriorate. LN2 vapour-phase containers with LN2 in the base of the freezer can maintain samples below T_g (glass transition temperature, i.e., -132°C) and submersion in LN2 guarantees a stable -196°C temperature environment for all samples. Some equipment uses LN2 as a coolant to permit storage temperatures in the -80°C range. Where a

regular supply and sufficient on-site bulk storage of LN2 are available, LN2 freezers reduce reliance on mechanical freezers and electrical power and guarantee sample integrity under critical temperatures during power cuts. Closed LN2 freezers can maintain samples at below -130°C for more than two months without the need to refill LN2. The initial investment and availability and cost of LN2 can be major drawbacks. Also, safety hazards inherent in the use of LN2, such as burning or oxygen deficit risks, should be managed. When LN2 freezers are used, oxygen level sensors should be used and replaced and calibrated every few years. The use of protective equipment, goggles and gloves in particular, should be mandatory, and these should be easily accessible. Appropriate training in the safe handling of cryogenics and of samples stored in cryogenics should be provided and included in an SOP describing the potential health hazards and required safety precautions.

Mechanical freezers

Mechanical freezers are used for a variety of storage temperature ranges and come in a wide range of sizes, configurations and electrical voltage. Ice crystal may form in biological samples at temperatures of about -70°C , therefore freezer temperatures should preferably be below -80°C . Cascade compressor technologies may produce temperatures as low as -140°C . Mechanical freezers, which generally require a lower initial investment than LN2 freezers and provide easy access to the samples, can be installed if electrical power is available. However, the compressor technology requires constant electrical power to maintain subzero temperatures, so a backup power system and an emergency response plan are needed. Whether samples get significantly warm during power cuts or freezer breakdowns depends on the temperature, nature and mass of the stored material, the ambient conditions and the design and maintenance of the freezer. Ambient temperature and humidity influence temperature stability considerably if doors are left open for prolonged periods, for example for sample loading, or if frost forms in the freezer, racks or samples. Overheating of compressors may shorten their lives. Mechanical freezers and refrigerators should be positioned with sufficient air flow around the units and preferably in rooms that are air-conditioned or have equipment for extraction of the hot air generated by the compressors.

Refrigerators

Refrigerators are commonly used where the longevity of the material being stored is enhanced by storage below ambient temperature. Storage at 4°C can also be an intermediate step before preparation for ultra-low-temperature storage. For refrigerators, as for mechanical freezers, it is important to maintain and monitor the temperature in the required operating range and to organize for a backup power plan.

Ambient-temperature storage

In the absence of mechanical or cryogenic equipment owing to practical or financial reasons, specific biological storage matrices may be used for long-term maintenance of some biological components at room temperature. Formalin-, PAXgene- or ethanol-fixed, paraffin-embedded tissues and lyophilized samples can be stored at such temperatures. The matrices should be evaluated before use to ensure that they are appropriate for downstream applications. Temperature, humidity and oxygen levels should be controlled to avoid mould growth and microbial contamination.

4. Information technology in biobanking

Information technology has a fundamental role in biobank organization. Indeed, software is already in use to guide biobank processes, drive quality assurance, optimize workflow efficiency, facilitate data utilization and maximize the use of collections.

Use of information technology in tumour biobanks

IT tools are particularly important in quality management of biological resources with respect to sample traceability, bioclinical annotation and issues relating to consent and ethics. The volume and size of primary and derived samples can be easily managed with IT software, and storage traceability information can show the current position and movement of samples in storage containers and records of all storage-related issues and incidents. Every process and procedure must be timed and recorded, providing information on operator, equipment and reagents. Each nonconformity item should be described by event, for example missing subject consent or deviation from protocol, and by status, for example if corrective action is awaited or has been taken. Sample collection, processing and preservation times provide important quality indicators for both fluid and tissue samples. Management of nonconformities is essential. A tool for automatic SPREC management is available on the ISBER web site (<http://www.isber.org/wg/bs/sprec.cfm>).⁽¹³⁾

Bioclinical annotations are a big factor in the quality of a tumour bank. Each sample must be characterized by standardized information based on dictionaries, thesaurus and international nomenclatures like the International Classification of Diseases for Oncology (ICD-O) or the Systematized Nomenclature of Medicine (SNOMED). Configuration of sample collection and sample reception forms, sample processing and anonymized sample distribution is a very useful feature for quality assurance. Software can also be used to manage donor consent if scanned copies of consent documents are saved and consent documentation is linked to patient data or their anonymized samples. A storage location tool can identify sample storage locations for new collections taking into account their numbers and the collection in which they will be included. Free space in storage containers can be identified to optimize the use of space. Specimen reception or sample distribution forms can be used and completed electronically following appropriate SOPs. This reduces manual input of data, saves time and is useful for quality assurance.

Data utilization

IT tools facilitate auditing of procedures, for example for nonconformity, and editing of activity reports based on queries, which can be saved. Files issued from these queries can be exported to a spreadsheet like Excel or converted into csv format for use with third-party software and to conduct statistical analysis. Files can also be printed via a text editor that is integrated into the software.

Optimization of biospecimen databases

A collection can be built up from biological resources selected for their common biological, clinical, and pre-analytical characteristics such as SPREC. The software permits the selection of a set of homogeneous or comparable resources and allows end-users to conduct research on cancer diagnostic or therapeutic biomarkers.

Biobank software

The use of software has ergonomic benefits because it reduces typing time. In particular, grouping of actions allows data input by sample batches to reduce typing time, especially for storage data. The software guides users on the different biobank processes including sample aliquoting, characterization, storage and management, and creation of derivatives. Software is useful also for cataloguing samples and managing their distribution. A catalogue is a special web tool that presents the list of the biobank's collections. Catalogues can be updated periodically by a formatted program issued from the biobank's database. The IT system tracks the distribution of samples and should have fields to enter dates of sample requests and transfers, parties involved, sample recipients and sample quantities requested, transferred or left in stock. The IT system will help to ensure that a minimum number of aliquots, as well as their adequate volumes, is maintained and stored for future use. A "return of research information" policy that allows data from experiments to be uploaded to the biobank's database will provide for continuous enrichment of the collection.

Types of information technology

Dedicated software. Tumour bank software must be selected for its security, robustness, interoperability and configuration features. The IT solution must ensure the security and accuracy of donor identification. Donors must be anonymized at all times. Hospital patients must be identified by their permanent ID numbers and their hospital visit numbers so that the samples can be linked to the respective hospital visits. Patient information must be protected to maintain confidentiality according to the standards of the Title 21 Code of Federal Regulations (21 CFR Part 11) of the United States Food and Drug Administration (FDA). Particular attention should be paid to genetic data. Software solutions based on web informatics systems are preferred for tumour banks as they offer high security. They also have the advantage of interoperability with other informatics systems. Maintenance and development of the IT application are largely dependent on its architecture and its ease of configuration and customization by its administrator.

Intermediate IT solutions. Off-the-shelf IT solutions include open-source software or tables. Open-source software solutions may appear to be free but have secondary costs. Therefore, it is important to assess the costs that may be described as expenses for “training” or “support” to set up the application or to export data, and those linked to eventual data migration to specific software. OpenOffice or Excel tables are other forms of off-the-shelf IT solutions. In making the decision on software, attention should be paid to the data items to be recorded, the quality of the data and the security of the application.

Data sets for biobanks

Data items to be recorded in a tumour bank database include:

- (a) Patient identification and demographic data, with sex and date of birth as well as state of the vital signs.
- (b) Diagnostic data with principal diagnostic end-point and date, and clinical tumour-lymph node-metastasis (cTNM) classification.
- (c) Specimen data, including identification details, sampling date, sample nature, organ from which sample was collected, collection method, stabilization process and preservation details.
- (d) Lesion data, including histological type, event nature, whether primary tumour or metastasis, and pathological tumour-lymph node-metastasis classification (pTNM).
- (e) Sample data—type, number, size, characterization (tumour, normal adjacent, normal distant, node, percentage of tumour, necrosis, stroma), and SPREC.
- (f) Derivative data, including type, number, SOP and characterization (e.g. concentration).
- (g) Storage data, including temperature, location (freezer, shelf, rack, box, position in box) and events.

All data items must be standardized to optimize their use and to allow their future export into a specific IT system. Using free text is not a good practice. All data should be entered through drop-down lists with standardized terms, preferably based on international nomenclatures such as SNOMED and CIMO. Tables do not offer data traceability, and one data item may be replaced by another without any alert by the application. To deal with this risk, it is important to keep different versions of the table or database with regular backup. Backup intervals could be daily, weekly or monthly depending on the volume of activity. A secondary copy should be stored separately, for example on a USB stick.

Quality is a constant concern in tumour banking for the biological resources, the bioclinical annotations and the IT system, which are the core elements of a biobank. The French standard NF S 96-900 (2002) describes the requirements for a quality management system for biobanks and biological resources. It aims to harmonize business practices and optimize exchanges between biobanks, and it includes requirements related to biobank IT.

5. Regulation in biobanking

The regulations governing biobanking need to address legal and ethical issues concerning the use of biological materials and data in cancer research. These regulations must deal with the rights and responsibilities of donors, biobank managers and researchers. Biobank governance must respect individual donors and guarantee their privacy and confidentiality. At the same time, it must not inhibit the provision of samples for potentially beneficial research. Regulations can be found dispersed in different declarations, such as acts governing the use of human tissue (<http://www.hta.gov.uk/legislationpoliciesandcodesofpractice/legislation/eutissueandcellsdirectives.cfm>; <http://www.info.gov.za/view/DownloadFileAction?id=105938>) and data protection (<http://www.doh.gov.za/docs/policy/2012/researchethics.pdf>). National human tissue acts (HTA) define human biological material (HBM), but in many cases they consider only tissue removed from deceased persons and may not include its use in research. Many countries in Africa have regulatory bodies with guidelines for the use of biological samples for research, such as the Department of Health (https://webapps.sph.harvard.edu/live/gremap/files/ke_NCST_guidelines.pdf), Department of Science and Technology, and Research Ethics Committee (<http://www.nhrec.net/nhrec/code.html>; <http://www.wma.net/en/30publications/10policies/b3/17c.pdf>). Where national guidelines do not exist, international guidelines can be used to address legal and ethical aspects concerning the collection and use of biological material and data for cancer research. However, traditional cultural values placed on HBM by local communities must be taken into account.

International guidelines

The Declaration of Helsinki ⁽⁴⁰⁾ refers to biomedical research on humans and specifies the provisions for use of human samples. It is intended as a gold standard for the ethical acquisition and use of samples, although it does not mention biobanking specifically. The United Nations Educational, Scientific and Cultural Organization (UNESCO) ⁽⁴¹⁾ emphasizes the protection of human genome-derived genetic data. The use of human biological resources and data for genetic research is addressed in the OECD *Guidelines on human biobanks and genetic research databases*. ⁽⁴⁰⁾

Governance

The key aspects relating to biobank governance are the policies, processes and procedures in place to ensure correct operation of the biobank. These should include oversight mechanisms for the development, implementation and use of the biobank; stakeholder support and accountability; and sustainability of the biobank. The responsibilities of funders, biobank developers, researchers and the various institutions involved must be clearly spelt out. For samples and data, there must be well-defined and documented processes for initiating collections, acquiring specimens and sharing samples. Oversight mechanisms should include ethics policies to ensure the ethical collection and use of samples and data, consistent with the consent granted by the subjects. Scientific policies should control the scientific validity of sample requests and consider the availability of samples and their rarity or scarcity. Data access policies should guide researchers' access to data and define the conditions for this and the review process. Governance processes must address the eventual winding up of the biobank and how samples and data will be disposed of or transferred to a third party. These processes must respect the initial consent granted by the donors, and disposal must comply with local regulations. Two documents set out the conditions for collection and use of samples: the informed consent and the material transfer agreement.

Informed consent

Informed consent is a fundamental legal and ethical principle in research biobanking. It underlines the basic rights of autonomy, liberty and dignity. It outlines the agreement between the donor and the custodian biobank on the provision of samples and data for research. Any deviation from this consent must be authorized by a supervisory board, such as an institutional ethics review board.

The basis of informed consent is that donors understand the request being made for storage and use of their samples and data. The consent form should be simple, clear and in the colloquial language of the donor. Consent must be voluntary and should indicate the purpose of the biobank; possible physical risks associated with collection of the sample; procedures for maintaining privacy; methods of protecting donor identity; future use of the samples and data; the right to withdraw consent and request destruction of remaining samples or render them anonymous; the possibility of sharing samples with other institutions, exporting them across borders or using them in commercially; and the right to refuse to provide samples, with clarification that such refusal will not affect the care to the patient. It is also necessary to indicate the possibility that the donor might be re-contacted for follow-up or more information or for further consent. It may be unrealistic to expect researchers to re-contact individual participants to obtain specific informed consent for each access to their samples in a new research project. In addition to being expensive and impracticable, such requests may also be against the wishes of the donor.

Types of informed consent

Several types of informed consent exist, defined by the level of permission from donors for use of their samples. Specific consent limits the use of the sample and data to a specific research project whose details are made aware to the donor. It is used when samples and data are identifiable. Partially restricted consent is used in a specific research project but allows future unspecified use directly or indirectly related to the research. Broad consent allows unspecified future use of the sample and data and the donor is provided with general information about possible future research, but which should comply with applicable national or local regulations and policies. Layered or tiered consent permits the donor to consent to particular aspects of the research but not others. Specific consent is advisable for identifiable samples and data, whereas broad consent may be used where samples and data are anonymized and the research is approved by an ethics committee or other body.^(43,44)

Vulnerable subjects

Safeguards should be put into place for the use of tissue from vulnerable donors, such as patients with mental incapacity, for example, heavily sedated people, people with dementia or impaired consciousness, and children. In the case of deceased donors, consent should be based on the views of the deceased person or of the family, if known. When research includes an ethnic minority, single community or cultural group, a representative from that group should be involved in the consent process.⁽⁴⁵⁾

Exceptions to informed consent

The need for consent can be waived by an ethics committee in accordance with applicable laws and regulations in cases where the researcher will not come into possession of identifying information and the specific research has been approved by a recognized research ethics committee.

Material transfer agreements

A material transfer agreement (MTA) is a contract governing the conditions under which samples and data may be used in research. It defines the rights and obligations of both the biobank and the receiving researcher. Provision of samples and data must be consistent with the given consent. Cross-border

collaboration and sample export must be governed by the permission from the informed consent and the local legislation, which will indicate whether biological material can be exported and what the necessary permits are.

An MTA should specify (a) the purpose of the transfer of the material and its intended use; (b) restrictions on the use of the samples, such as their redistribution to third parties or sale for commercial purposes; (c) restrictions on re-identification, where de-identified specimens are provided; (d) requirements for handling biosafety hazards; (e) disposal or return procedures for unused samples; (f) ownership of intellectual property rights; (g) acknowledgement arrangements and publication rights; (h) provision of aggregated or raw research data; (i) guarantees and waivers; and (j) other factors that may govern sample transfer and the applicable regulations and law. The specific protections for data may be included in the same MTA or a separate agreement. Such an agreement must deal with the future use of the data, including their possible redistribution, requirements for maintaining privacy and confidentiality, access to data and protection of data against unauthorized access.

Data privacy and data protection

Data protection is a key principle in protecting donor privacy and confidentiality.⁽⁴⁶⁾ The types of data collected by the biobank are (a) sample-related data on quantity, quality and methods of collection and storage, and (b) donor-related data on clinical, pathological and lifestyle aspects. These data are considered sensitive because they provide information for potential identification of the donor and possible familial indicators. Therefore, procedures must be put in place to store data in a manner that protects the identity of the donor, including de-identifying or coding any identifying data, storing samples without associated identifying data, and ensuring that data are stored securely with access restricted to authorized personnel, including access to coding keys that may re-identify data or associate them with other data sets.

Sample identification

Identifying information should not be provided to researchers unless the research specifically requires it and approval of either the donor or the ethics committee has been received. If identifiable samples are used for research, donors should be informed about any implications, for example if they will be re-contacted by researchers or receive feedback or requests for access to medical records.

Genetic data

In cancer research, genetic data should be defined as somatic or germline. Somatic alterations are genomic anomalies that are confined to cancer cells and have the potential to provide valuable diagnostic, prognostic and treatment information. Germline variations are gene variants that increase the risk of cancer either related to hereditary predisposition or promoted by lifestyle and environmental exposures. These data are together considered “genetic data” and as such require specific consent, because they are considered as sensitive identifying material with consequences not only for donors but also for others in their families. Particular attention needs to be paid to the protection and release of these data⁽⁴⁷⁾. A dedicated data access committee should make the decision about providing genetic data to the general research community. Complex ethical issues such as whether to provide genetic and genomic research information to donors about heritable factors or disease risks mean that biobanks should choose to error on the side of caution, and these data should remain in the domain of research unless validated and used in a clinical context.

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Chapter 8

Pathology

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Chapter outline

1. Introduction
2. Laboratory space design process
3. Histopathology services and laboratory set-up
5. Management responsibilities

1. Introduction

An efficient and reliable pathology service is the cornerstone of illness diagnosis and provision of adequate tissue preservation for research. In essence, excellence in diagnosis is a core requirement for patient care, teaching and research. It also provides the gold standard for evidence-based health statistics. Pathologists, in addition to diagnosing the individual patient, play a crucial role in defining disease patterns in susceptible populations and describing pathogenesis.

In setting up pathology resources for research, every pathology laboratory system must have the mission or goal of making the provision of accurate and timely cancer diagnosis a top priority. In the process of conducting a diagnosis, tissue handling and processing must be streamlined to ensure proper tissue archiving for future analysis or research studies. Tissue blocks and slides provide a permanent record that can be kept for decades for re-evaluation of patient diagnosis or for research. The process starts with tissue handling from the time of surgical resection to tissue reception in the laboratory and subsequent processing for diagnosis. This process must be based on very clearly written standard operating procedures with assurance that everyone at all levels will adhere to the protocols. A well-designed system for pre- and post-analytic procedures should be established by hospital surgical and pathology departments to ensure proper sample collection, preservation, processing and review, and reporting of results in a timely fashion.

Properly functioning pathology services are part of the overall patient care structure and are linked to medical records and clinical decision-making. For this reason, accurate and consistent tissue diagnoses are the foundation of cancer registration, an instrument that depicts cancer rates and therefore informs the plans of policy-makers for cancer control and allocation of services.⁽¹⁾ Quality assurance is essential in all steps in the process to improve the accuracy of the diagnosis, as well as ensure the validity of the material and information to be used for registries, research or biorepositories. Studies show that investment in the quality of specimen collection, diagnosis and reporting processes results in overall cost-saving by reducing improper therapy and adverse outcomes.

Ultimately, the laboratory must be credible internationally and deemed satisfactory for both local and international collaborative studies. Proving adherence to internationally acceptable standards may require participation in international and national laboratory accreditation programmes.

2. Laboratory space design process

The laboratory design process requires a definition of each of the steps in tissue processing and ultimate diagnosis followed by the assignment of adequate space for each of these functions. Each space needs to be configured based on its proposed function with appropriate furniture and airflow provisions. Areas earmarked for tissue grossing will be expected to have high levels of formalin fume. In such a case, there will be the need to provide for adequate ventilation. Manufactured grossing stations with vents leading to the exterior are most suitable, if they are affordable.

The design process must also define and optimize workflow, including the sequence of specimen collection, reception and registration and tissue processing for routine hematoxylin and eosin staining, which can be done manually or using an automatic stainer, if it is affordable, especially for big sample volumes. Special histochemistry and immunohistochemical staining processes are best carried out in assigned spaces depending on availability of staff and space. It is also important to provide for safety during the design process. Eyewash stations and emergency water shower stations are critical for decontamination of staff after accidental spills of chemicals. Diagnosis is done by professional personnel who are trained pathologists, and ultimate reporting will require adequate support staff for transcription and appropriate record keeping.

3. Histopathology services and laboratory set-up

This process will include appropriate stocking of the laboratory with reagents and chemicals and establishment of a purchase process for their replenishment before they are exhausted. Standard operating procedures, logs and forms must be properly designed to capture all relevant information for tracking of individual specimens throughout the entire laboratory process and for the extraction of information for determining turnaround time. A computer-based record management system will require investment in laboratory management software, servers and reliable information technology support. The benefits of such a system with its excellent information retrieval will ultimately justify the upfront set-up costs and should prove to be a wise investment.

Pathology laboratory systems invariably generate biohazardous waste. Provision for appropriate waste removal or disposal is an important component of the set-up process. The needs of surgical pathology systems include appropriately providing for (a) routine and special procedures, (b) efficient transfer of material to pathology laboratories, (c) receipt and documentation of specimens, (d) efficient case tracking, reporting and archiving, (e) basic working equipment for tissue evaluation and processing, (f) uninterrupted supply chain for quality reagents and equipment, and (g) equipment maintenance.⁽¹⁾

The key to maintaining high tissue quality for diagnosis and research is proper preservation of both tissue form and content. Optimal fixatives must preserve the tissue macroscopic and ultrastructural morphology, as well as the biochemical integrity of proteins and nucleic acids. Although toxic, formalin (10% formaldehyde in 0.1M phosphate buffer to pH 7.4) has remained the most widely used and most versatile tissue fixative.

Tissue processing for diagnosis and archiving for research¹

The ideal tissue is “one that carries a complete and unaltered representation of the tissue in vivo”, that is, preservation does not alter the nucleic acids such as DNA and RNA or the proteins in the tissue. Since perfect preservation is probably an impossible goal, we can only aim to be as close to it as possible. Many challenges affect the ability to provide optimal preservation of tissue quality, particularly for research, including:

¹ Chapter 7 provides a detailed review of specimen collection and storage for biobanking.

- (a) Tissue type. Some tissues degrade faster than others, such as liver and pancreas compared with lung, due to inherent differences in their nuclease content.
- (b) Pre-excision hypoxia related to the presence of hypoxia-inducible factors that alter the gene expression profile or induce cell degradation or death.
- (c) Length of storage.
- (d) Freezing and thawing factors.
- (e) Tissue preservation methods such as freezing, fixation (including formalin and ethanol fixation) or preservation in a proprietary solution referred to as RNAlater.
- (f) Nucleic acid and protein extraction methods. Some methods for DNA or RNA extraction are less effective in separating proteins from DNA, resulting in inhibition of polymerase chain reactions or other enzymatic manipulation of DNA or RNA. The length of fixation affects the quality of the tissue for IHC-based studies, so breast prognostic marker protocols have very stringent requirements for length of fixation.⁽²⁾ New techniques allow for enhanced retrieval of antigens in IHC and genetic material for molecular studies.⁽³⁾

Optimal tissue preservation methods

Tissue preservation is the essential and ultimate goal of tissue archiving. There are a number of requirements for any tissue preservation method. It is important that the chosen method of necessity induce quick inactivation of degrading enzymes to preserve tissue and nucleic acid integrity. In this light, the optimal method for tissue preservation is cryopreservation. This entails maintaining the tissue at -80°C for a short period or at -135 to -140°C in liquid nitrogen for long-term storage. In a low-resource environment, using cryopreservation as the sole method of tissue preservation for research can be difficult and potentially unrealistic.

Alternative tissue preservation methods

In resource-poor environments with inadequate or erratic power supply and no consistent backup power generator and where liquid nitrogen is either unavailable or in short supply, alternative tissue preservation methods are needed.

Tissue fixation

Tissue fixation is a major resource for molecular biologic studies in all settings. Advances in technology and applications of PCR and RT-PCR make it possible to apply a majority of molecular techniques to fixed tissue, including microarray analysis, as well as quantitative and qualitative DNA, RNA and miRNA studies. Fixation methods include:

- (a) Formalin fixation (non-buffered): While formalin (non-buffered) fixed DNA is adequate for histology, tissue preservation in this medium is suboptimal for molecular studies such as DNA sequencing because mutation artefacts are introduced into the DNA by formalin fixation at acidic pH. Such DNA have higher rates of depurination at low pH fixation, which favours misincorporation of noncomplimentary nucleotides (cytosine in place of thymine) at apurine and apyrimidine sites. It also causes degradation of DNA into very small fragments.
- (b) Formalin fixation (buffered 10%): Buffered formalin is excellent for morphology. In addition, in buffered 10% formalin (10% formaldehyde, 0.1M phosphate buffer to pH 7.4), artificial mutations are less frequent than in non-buffered formalin. However, PCR products are often limited to low molecular weight DNA (< 500 bp) due to scission of the phosphodiester backbone of DNA during fixation. If formalin is the only viable option to fix tissue that may potentially be subjected to future molecular studies, then it is recommended to (a) cut the tissue into very thin sections and limit the fixation lag time

to less than two hours, (b) use cold 10% neutral formalin, if possible at 4°C, (c) use EDTA (anti-nuclease) at 20–50 mmol/L as an additive, (d) avoid low pH and high humidity environments, and (e) avoid prolonged storage of the tissue in formalin.

- (c) Alcohol fixation: In general, alcohol fixatives give reasonably good morphology and excellent nucleic acid preservation outcomes. Examples of alcohol preparations include 70–100% ethanol or methanol, Carnoy's fixative (60% ethanol, 30% chloroform and 10% glacial acetic acid), and Methacarn (60% methanol, 30% chloroform and 10% glacial acetic acid).
- (d) RNAlater: This is a proprietary aqueous solution from Ambion, Inc. that has been shown to provide excellent preservation of DNA, RNA and proteins. It is stable at room temperature so it can be used to preserve tissues in ambient temperature if facilities for storing tissue at -20°C or -80°C are not available. Owing to that versatility, RNAlater is associated with several advantages, including ability for immediate RNase inactivation, freedom from the need to use liquid nitrogen and freezers, elimination of freezing and grinding, ease of adaptability for field collection of tissue samples, flexible tissue storage, and compatibility with most RNA, DNA and protein isolation procedures.

Other issues relevant to laboratory set-up

An essential part of the set-up of pathology services is the incorporation of quality assurance measures into daily activities so that they become part of the procedures. They should be a habit not an afterthought or an often-neglected added duty. For tissue and cytological diagnoses, quality begins at the point of specimen collection and includes adhering to the standard operating procedure manuals and managing supplies. There should be mandatory training of personnel at all levels in the use of checklists based on SOPs to ensure quality control of specimen collection, fixation, processing, sectioning and staining. Quality assurance of diagnosis encompassing internal and external review, documentation of errors with remediation, and on-site assessment by national or international accreditation agencies is important in ensuring excellence in the pathology processes.

The following section presents the starting points for developing SOPs, highlighting areas with the most significant impact on the quality of pathology services.

Point of sample acquisition, such as a surgery, clinic or external source

Patient and sample identification

- (a) Unique identifiers are the ideal method for maintaining the integrity of patient information and material. The hospital or clinic should have a standard system for maintaining a complete medical record on a patient that carries over from one admission function to the next. Electronic medical records, when and where they can be used, help to ensure that information is consolidated and up to date and allow computer generation of labels such as ID numbers, printed sample labels and barcoding, which help to avoid clerical errors and increase efficiency of service.
- (b) In most hospital and clinic settings, specimens are collected and placed in containers with a fixative at the point of acquisition and then transported to the pathology department for evaluation and sectioning in preparation for processing. Material collected in the surgery through biopsy or for cytology should be placed in containers with properly verified patient identification. Appropriate paperwork should accompany the specimens, and the completeness of the information should be checked prior to sending out the container.
- (c) If samples other than for routine formalin fixation are needed for testing or inclusion in a biobank, additional procedures and supplies need to be determined and put in place before procurement of the specimens. Patient identification or study code labels should be affixed on the storage container at the time of tissue collection.

Sample handling

- (a) Rapid and appropriate sample fixation is essential for quality diagnosis. Standard, easy-to-follow instructions with illustrations should be displayed where they are clearly visible to the trained personnel as they handle specimens.
- (b) Ensure that adequate collection containers of appropriate size and with secure closure are provided for all services, whether internal or external, for submitting pathology specimens to the laboratory. The ratio of tissue volume to fixative should be 1:10.
- (c) Small specimens can be placed directly into formalin or another fixative and transported to the laboratory. Larger specimens, especially those with a capsule or unexposed lumen, need to be opened or cut up to ensure uniform penetration of the fixative. This requires that the pathologist or trained pathology assistant be available on site to properly examine and document findings before any sectioning is done. Alternatively, the specimen can be transported to the pathology department within two hours. The time fixation was initiated should be recorded.
- (d) If fresh tissue is needed for a research protocol, trained personnel should be available to examine the tissue, document the findings and take samples, making sure that priority is given to the portion to be sent for routine diagnosis. Many lesions are not uniform and care should be taken to insure that the lesion in the diagnostic sample is the same as that used for research.

Systematic delivery of samples to department of pathology:

- (a) Develop a system to pick up specimen from the hospital and clinics at least one or more times per day, depending on the need. The laboratory courier should ensure that the container and volume of formalin are adequate and that request forms are filled out correctly. To ensure accountability, a recording system should be in place at the point of collection.
- (b) An important recommendation is to eliminate the practice of giving specimens to patients to deliver to the laboratory unless the patient or a family member specifically requests the specimen to take to a private laboratory.

Personnel

The laboratory staff must include a histotechnologist trained in the art of tissue processing, the use of the microtome and the techniques of tissue staining and immunostaining. Laboratory aides or assistants can be hired to assist the professional technical staff as may be appropriate.

Equipment

Basic equipment includes an automated tissue processor, an embedding centre, a microtome, a cryostat, a temperature-adjustable water bath, a fume hood, a 4 °C refrigerator, and -20 °C and -80 °C freezers. Manufactured or commercial grossing stations, routine slide stainers and immunostainers may be desirable but are not considered basic equipment for a resource-poor environment.

Ongoing service support

Maintaining appropriate and continuous supply of consumables remains a challenge in resource-poor environments. Adulteration of simple reagents such as formalin, xylene and alcohol by suppliers is common and requires eternal vigilance.

The process

Receipt of a case in the pathology department and case tracking from gross examination and sectioning to signing out and reporting should be logged into a laboratory information system. Electronic records are optimal but not always available. SOPs and checklists ensure that the processes are uniform and significantly reduce errors. An ongoing quality assurance procedure and training of personnel to prevent problems and to take corrective action as needed are good practices.

Case intake

- (a) Validate and document the specimens.
- (b) Log in specimens with time and date, label all the components whether documents or samples, and verify that case numbers are unique and sequential.
- (c) Check pathologists' or pathology assistants' schedules for grossing (cut-up) duty and assign the case.
- (d) On a regular basis deliver material to the grossing area and notify the appropriate personnel.

Grossing (cut-up)

- (a) Process specimens in a timely fashion throughout the day.
- (b) Verify specimen type, time and date it was collected and clinical information against the request form. Contact the referring clinician if there is any discrepancy.
- (c) Ensure levels of formalin in containers are adequate, and assess the status of fixation.
- (d) For gross description and sampling:
 - (i) Create and provide in the cutting areas standardized protocols for case evaluation, description and sampling, and in staging criteria for oncology specimens.
 - (ii) Avoid carrying over specimens between cases, especially small biopsies, by having one case open at a time, rinsing cutting areas with cleaning solution, and cleaning or replacing cutting boards as needed.
 - (iii) Prepare and properly label cassettes. Trained assistants can improve efficiency and accuracy in this step, so they should be made available for large or complex cases. Colour-coded cassettes may be used to distinguish samples for specific protocols.
- (e) The samples taken should fit easily into the cassette and should not exceed 2 mm in thickness for optimal fixation.
- (f) If appropriate, samples can be taken at this time for biobanking or for approved research according to established protocols.
- (g) The remaining material should be replaced in tightly sealed formalin containers and stored for easy retrieval until the case is finalized.
- (h) Old cases from the cut-up area should be moved to permanent storage or discarded following biosafety guidelines.

Histology laboratory

The histology laboratory is used for processing, embedding, sectioning and staining of tissue samples for review by pathologists. SOPs and checklists for each step are essential for efficient, high-quality workflow and products. The equipment should be regularly maintained, reagents need to be kept in good supply and best practices need to be established and used at all times. Excess heat or exposure to xylene and high-percentage alcohol can damage tissue and render the proteins inadequate for evaluation.

Processing

Ensure that adequate amounts of fresh, clean reagents are used in the tissue processing stations. Before placing cassettes on the machine, check to be sure they are properly closed and that there is no material floating in any of the solutions that might contaminate the tissue block.

Backup electricity sources need to be available.

Embedding

Use labelled cassettes with clean paraffin. Skin or gastrointestinal biopsies should be oriented in a way to ensure proper assessment of epithelial surface, that is at right angle to the plane of sectioning.

Cutting stations

Each station should have a microtome with smooth (preferably disposable) sharp blades, a water bath, adequate supply of slides and slide racks.

Process only one case at a time.

Clean the water bath after each case.

Staining

Staining solutions need to be fresh or filtered, and rinse solutions must be changed as needed. Cover slips should completely cover the tissue section and bubbles should be avoided in mounting fluid.

Each department of pathology needs a system of block and slide storage for preservation and retrieval of material.

Case review and signing out

Timely review and reporting of cases is an essential part of patient care. Delaying the diagnosis means delaying appropriate treatment, or worse, treatment without the benefit of the pathology results. Guidelines should be established based on the type of specimen and other factors determined by the pathology laboratory and clinical services. In general, small diagnostic biopsies should be reported to the clinician within 48 hours. Turnaround time (TAT) for larger specimens can vary.

Sign-out rotations should be established within the department to include all staff and, where present, residents such as postgraduate trainees. Typical training institutions assign slides to the postgraduate trainees for initial review and study of the literature for one day. Attending pathologists supervising the trainee are responsible for the final report. Additional studies are requested if required, for example for special stains or IHC. Depending on the length of delay, a preliminary report may be issued to ensure adequate TAT.

Validate the details and specimen identification and quality of slides. Clerical and cutting errors such as specimen mix-up or poor staining etc. and corrective action taken should be documented.

Pathology reports should:

- (a) respond to clinical questions;
- (b) direct patient care;
- (c) include information regarding staging and prognosis;
- (d) suggest etiology;
- (e) describe host response;
- (f) give a differential diagnosis.

As a general recommendation, establish internal quality control for quality of material, clerical errors, and diagnostic accuracy. The standard guideline for case review is 10% of cases per pathologist. Define the procedures for resolution of difficult cases or lack of consensus.

Use of telepathology or digital images for external consults can be implemented as a local, regional or international process. Legal and ethical guidelines should be established by the institution for reporting of opinions from non-staff members.

Use slide boxes to save specimens for teaching, and provide controls for special stains and immunostains.

To subscribe to quality assurance needs, external quality assurance programmes should be followed by staff and postgraduate trainees. Guidelines for specimen use for future education research work need to be established.

Case reporting

Final case reports must be written and signed by a certified pathologist and reported within a period of time appropriate for adequate patient care. Unexpected or urgent findings should be communicated in a manner that shows the pathologist that the results are made known to the treating physician as soon as possible. Standard processes should be established for delivery or pick up of reports and their inclusion in the medical records. Additional use of diagnostic reports or case information in cancer registries or for research should follow approved protocols.

Quality assurance and quality control for the pathology laboratory process

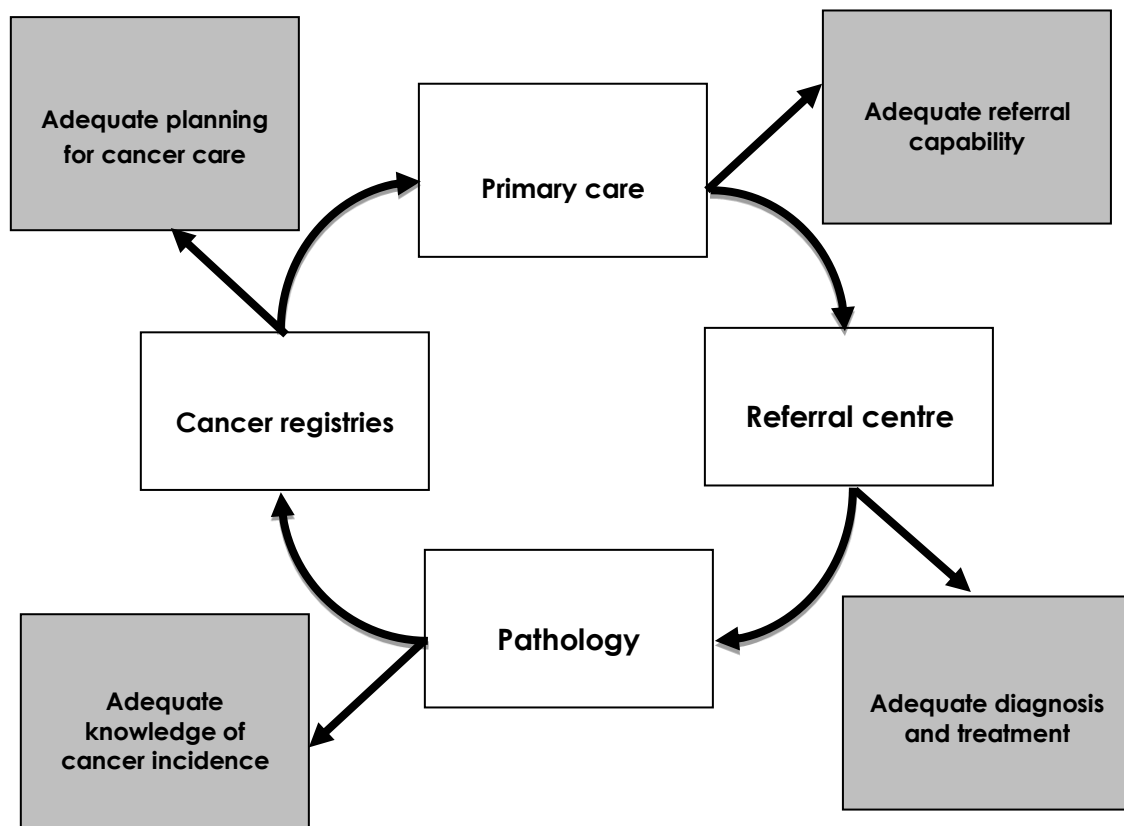
The standard of excellence required for a pathology research laboratory should not be different from that for a clinical pathology laboratory. The quality assurance processes used can be internal or external. Internal quality procedures should be built into the entire process of operation and are designed to detect irregularities and potentially serious errors when they occur. External quality procedures are designed to ensure that the performance at every level of operation in the laboratory is comparable to what obtains in other laboratories within or outside the country.

4. Management responsibilities

Planning for cancer research activities in Africa should be a multidisciplinary activity geared at strengthening health-care systems, starting with the main referral and teaching institutions. The necessity to meet the mandatory requirements of functioning equipment, consistently available supplies, documentation of and training in pre-analytical and analytical procedures, and well-established quality assurance systems must be communicated to decision-makers at the national health services and ministry of health, as well as clinicians and researchers. Local, regional and international boards can provide guidance on standards and guidelines for best practice for various resource levels. For example, the Breast Health Global Initiative (BHGI), which is a multinational multidisciplinary group, over the past decade has developed guidelines for breast cancer detection, diagnosis and treatment in low- and middle-income countries. One of its subcommittees specifically focused on pathology guidelines for breast specimens.⁽⁴⁾

Pathology deals with many investigation classifications including for benign and malignant neoplasms, infectious and environmental etiologies, chronic disease, reproductive conditions, congenital abnormalities, degenerative conditions, trauma, and forensic sciences. If pathology activities are not conducted properly clinicians will be misled, patients will suffer from receiving the wrong treatment or no treatment at all, and registry or epidemiological data will be incorrect and unreliable. Above all, resources will be incorrectly expended or wasted (Figure 1).⁽⁴⁾

Figure 1: Central role of pathology in clinical care, research and public health in sub-Saharan Africa



Box 1: Essential ingredients of effective pathology services

Systems needs

- (a) Appropriate and timely fixation for routine and special procedures.
- (b) Efficient transfer of material to pathology.
- (c) Efficient systems for receipt and documentation of specimens.
- (d) Case-tracking process.
- (e) Reporting process.
- (f) Archiving process.
- (g) Basic working equipment for tissue evaluation and processing.
- (h) Uninterrupted supply chain for quality reagents, and equipment procurement and maintenance.

Quality assurance needs

- (a) Standard operating procedures and training of personnel at all levels on their use.
- (b) Quality control of specimen collection, fixation, processing, tissue sections and staining.
- (c) Quality assurance of diagnosis conducted internally and by an external reviewer.
- (d) Documentation of errors and remediation.
- (e) On-site assessment.

Workforce needs

- (a) Advocacy to highlight the importance of pathology among the national health services, ministries of health, policy- and decision-makers and clinicians and to ask for the needed personnel and other resources.
- (b) Histo- and cyto-tech training.
- (c) Bursaries for pathologists to attend relevant professional meetings.
- (d) Opportunities for exchange of slides or other training materials through a clearinghouse centre that can coordinate this.
- (e) Telepathology as a short-term solution to provision of education, training and consultative and primary diagnostic services. Telepathology should not be treated as a panacea for closing the skills gap.

Note: Clinical care at all levels depends on a functioning system that has referral and feedback mechanisms. As shown in this figure, effective primary care provision must be informed by knowledge of disease prevalence and diagnosis and there should be a provision to refer complicated cases for specialized care. Referral centres require comprehensive diagnostic and treatment facilities and equipment. The information generated needs to be tabulated, published and used to inform policy and practice at all levels of the health system.

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Chapter 9

Data management and analysis

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Chapter outline

1. Background and introduction
2. The African setting
3. Infrastructure

1. Background and introduction

Sound management of data is essential in any research project. Without data that are carefully collected, securely stored, well maintained and robustly analysed the research enterprise will be severely compromised. There are many things to consider when planning for data management and analysis in the context of a research project. These include not just technology, such as software, hardware and network connections, but, most importantly, people. Investigators, research staff and analysts are vested with the responsibility of selecting and using the best methods for collecting, managing and analysing data. Seldom is it the case that poor data quality or inaccurate analyses are the fault of the technology, even in the case of equipment failure, which should be foreseen with careful planning by people. We dedicate much of this chapter to a discussion of various technological solutions to problems that need to be dealt with in any research project.

In this chapter we will describe the ways in which the problems of data management and analysis have been addressed in various countries in Africa. There are some common elements in the situations in these countries, such as the need for research staff trained in information technology and for improved information infrastructure. But it is enlightening to see the array of solutions that have been proposed and in most cases used successfully. We will also describe the infrastructure in many countries in Africa that supports research data management and analysis. Finally, we will look at best practices for data management and analysis.

2. The African setting

Over the past decade there has been considerable activity in the domain of data management, particularly as it applies to research or clinical and public-health data, which are often used for research purposes. We provide here a brief review of this activity in Africa as reported in biomedical literature.

Data quality

The quality of research data is a major concern everywhere, and Africa is no exception. Numerous reports have indicated that the quality of data from registries and hospital records and primary data collected specifically for research purposes can be quite substandard and, thus, difficult to analyse. Issues with data quality pervade the landscape of research in Africa. One study on routine prevention of mother-to-child transmission (PMTCT) of HIV found that 50% of needed data were missing from the reports to the district health information system in Kwazulu-Natal, South Africa.⁽¹⁾

Data quality is very much an issue when data are collected on computing devices such as tablet computers or smart phones. Telemedicine and eHealth systems that use hand-held devices for data collection are prone to poor data quality control unless specific measures have been incorporated into the device software. One such approach is being used for telemedicine efforts in western Kenya ⁽²⁾ and it involves creating a data integrity module that enforces data quality checks in data management systems. Another measure, to employ periodic data audits, is being used in the prevention of mother-to-child transmission of HIV.⁽³⁾ Ongoing, onsite staff training was found to improve the quality of data collected during voluntary counselling and testing for HIV in Kenya.⁽⁴⁾ A hybrid approach to data entry was used in Botswana, where some data were entered directly onto a computer while other data were entered from paper forms using optical character recognition software.⁽⁵⁾ This seemed to be a reasonable approach that considered the high demands on clinicians' time as contributing to data-entry errors.

Data integrity is not the only quality issue in data management in Africa. Data management software can be a source of the problem. In Tanzania, data management software deployed in district health information systems was rated very low in usability, and could not map to paper-based data-collection forms.⁽⁶⁾ The deployment of sophisticated information systems in institutions where staff lack the required training and experience to use these systems contributes greatly to the poor quality of the data.⁽⁷⁾

Sources of data for research

When data are collected specifically for a research project, that process is usually referred to as "primary data collection". These data account for a large portion of all research data. For example, data management systems have been used to support clinical trials ^(8,9) and survey studies.^(10,11) But researchers often turn to existing data sources such as medical records or disease surveillance data in order to carry out their research quickly. Electronic medical records in general are becoming increasingly common in Africa.⁽¹²⁻¹⁶⁾ OpenMRS is an open-source electronic medical record system that is used extensively in Africa.^(13,17-19) It is highly customizable and can be maintained at local clinical sites and used by the staff, a probable reason for the satisfaction with this software. However, some requirements limit the use of OpenMRS to sites that are able to bring in expert developers. Although not usually thought of as research data management systems, OpenMRS and other electronic medical record systems are extremely rich sources of research data and, therefore, those responsible for their design and use should consider the needs of the research enterprise.

Disease surveillance data management systems

Researchers should not overlook the value of data management systems that capture vital statistics or disease registry data.^(17,20,21) Numerous disease surveillance systems have been used throughout Africa and they are extremely rich sources of data for research.^(17,20-25) Although these systems have had a poor history, especially in terms of completeness of data, some efforts to improve their data quality have been successful.⁽¹⁷⁾ Microsoft Access has been used in a multitude of research and disease surveillance studies such as the tuberculosis contact tracing project in the Gambia.⁽²⁶⁾ MySQL has been used to support a registry of neglected tropical diseases.⁽²²⁾

mHealth

Mobile health computing, commonly referred to as mHealth, is a rapidly growing domain of informatics. mHealth is used in a variety of applications ranging from mobile phone use to improve point-of-service data collection, care delivery and patient communication, to use of alternative wireless devices for real-time medication monitoring and adherence support.⁽²⁷⁾ mHealth is especially prevalent, and increasingly so, in Africa, where the smart phone and tablet computer technologies are well supported by wireless telecommunications networks. Mobile phones have been used in Senegal to disseminate health information ⁽²⁸⁾ and in other countries such as Botswana to collect data as well.⁽⁵⁾ Mobile technologies may solve one of

the most difficult problems facing global health efforts, that of structural barriers to access health care, by eliminating or at least minimizing the communication gap between rural patients and urban medical specialists.⁽²⁷⁾ The capacity of mHealth approaches to more rapidly deliver highly specialized care, including radiology, dermatology and oral medicine to distant sites has been well demonstrated in Botswana—a vast country with a small health-care workforce that faces the challenge of delivering health care to a relatively small population that is spread out around the country.⁽²⁹⁾ However, while enthusiasm for effective mHealth interventions in sub-Saharan Africa is high, little is known about their efficacy or effectiveness, and we support the call of others that a better evidence base is needed to critically interrogate the role of mHealth on the African continent and then to use this evidence base to effectively implement the highest impact mHealth solutions.⁽²⁷⁾

3. Infrastructure

Resource and infrastructure conditions vary greatly across the African continent. South Africa has well-developed infrastructure including a national health informatics association (<http://www.sahia.org.za/>). But even in South Africa infrastructure varies greatly between urban and rural settings. In the less industrialized African countries the infrastructure is mostly in poor state.

Collaboration with local investigators is a crucial component in conducting a successful research project in a global setting. The reasons for this are many. The local investigators have expert knowledge of their setting's infrastructure. A detailed discussion with the local investigative team on what is known of existing infrastructure will inform the decision on the choice of data tools to use in a particular setting from the available options. Depending on the planned approach, communication with relevant in-country industry leaders may prove fruitful for the researcher in the planning phase. Such leaders include cell phone companies' management, local IT consultants and developers, and local or national universities, particularly their IT, library science and computer engineering departments. If new technologies are planned, then having a tech-savvy, cross-cultural, skilled and diplomatic implementation manager will greatly expedite the project and enhance the chances of success.

If suitably skilled staff are not available, researchers and their core staff should acquire the necessary skills on their own through data management educational programmes at the growing number of institutions or through online programmes that offer a range of such opportunities from single courses to master's degrees. The American Medical Informatics Association has an excellent resource on these programmes in the United States (<http://www.amia.org/education>). A leader in this area in Africa is the University of Kwa-Zulu Natal through their medical informatics programme (<http://telehealth.ukzn.ac.za/Programmes/MedicalInformatics/MastersInMedicalScienceMedInf.aspx>). Our experience with this group is that they are highly collaborative and well equipped for developing informatics infrastructure on the continent.

The final choice on the database system to use depends on a number of factors, including careful consideration of what will be supportable by local infrastructure and staff skill sets. However, innovation, including introducing new, more advantageous systems to the African setting, as well as staff training, should be encouraged. The key is to innovate with in-depth knowledge of the local infrastructure to ensure that the chosen solution serves the project's needs while also being both implementable and maintainable.

4. Best practices

The best practices of research data management and analysis involve careful consideration of the data management needs in all the stages of a research project from conception through to final data analysis and reporting. We provide here a description of these practices and the resources that should be considered to meet the requirements of these practices. Of paramount importance, however, is to seek data management

and analysis collaboration with African-based institutions. This will facilitate development of African-based analyses as well as general collaboration across institutions, thereby promoting academic cross-pollination. In addition, sharing of software and approaches, where possible, will enrich all involved.

Research conception

Research conception is the earliest stage of a project. It is often tempting to immediately think about the software or hardware to use or purchase for a project as soon as that project is conceived. We strongly suggest that researchers defer this decision until well after the project is thought through. Nothing will be lost but there is much to be gained if you delay this decision to until after you have written the data management and analysis sections of the proposal or protocol at the very least, and certainly after you have developed the specific aims and methods. The reason for this is that it is very easy to be lulled into a particular path of managing and analysing research data by the computing and other resources on hand at the time the project is conceived. But we see time and again that this path is usually a tortuous one, requiring many amendments to the data analysis methods as the project is revised. It is best to put off thinking about the resources for data management and analysis until the end, when the requirements of the project dictate the software and hardware needs.

Database design

It should be assumed that the research data will be entered into a database. This database is simply a two-dimensional table or set of such tables in which a row represents a record and a column represents a specific field or variable. Table 1 shows the basic architecture of a database table.

Table 1: Example of a database table

| Subject ID | Birth date | Sex | Clinic |
|------------|------------|--------|-------------|
| 1 | 5/1/1940 | Male | Medicine |
| 2 | 7/12/2001 | Female | Paediatrics |
| 3 | 10/12/1983 | Female | Obstetrics |

Careful modelling will ensure that the database is well designed and therefore easy to use, and that it can support the data management tasks of data entry, editing and export for analysis. Without a good data model, it is probable that these tasks will be compromised.

Data modelling

At the heart of research data management is a database. Research data require careful consideration of the database structure. We approach database structuring through a rigorous modelling exercise that, when done correctly, will lead directly to a robust database design that will facilitate data entry and export with minimal data loss or corruption. Without such modelling, one risks developing a database that makes it impossible to create analysable data sets. It is beyond the scope of this chapter to provide a comprehensive tutorial on data modelling, but we can address the most important problem that persists in research data, and that is the so-called “multivalued attribute” and its related anomaly, the “repeating group”. This problem involves the collection of the same data more than once. An example would be a set of diagnoses noted for a research subject’s hospital stay that is represented by a researcher as diagnosis 1, diagnosis 2, diagnosis 3, and so forth. Assuming that all these are at the same level and that none of them is a primary diagnosis or is ranked otherwise, these diagnoses represent the same concept: discharge diagnosis. Yet, that concept is represented multiple times in the data (shown in Table 2 as ICD-10 codes) as a group of columns in a spreadsheet or other type of table.

Table 2: Example of ICD-10 Codes

| Subject ID | Diagnosis 1 | Diagnosis 2 | Diagnosis 3 |
|------------|-------------|-------------|-------------|
| 1 | A15.0 | T12.9 | C61 |
| 2 | I06.2 | A53.0 | E11 |
| 3 | B17.1 | D57.1 | J42 |

The problem is that if you wanted to identify all those who had tuberculosis of the lung (T15.0), you would need to search through all the “diagnosis” columns to find the code that indicates the presence of that diagnosis. This is cumbersome and inefficient, but also can lead to inaccuracies. It is best to represent discharge diagnosis as a single field or variable in the data, where each diagnosis is represented as a separate row or record in the data not as a separate column (Table 3).

Table 3: Example of diagnosis represented separately

| Subject ID | Diagnosis | Diagnosis 2 | Diagnosis 3 |
|------------|-----------|-------------|-------------|
| 1 | A15.0 | T12.9 | C61 |
| 1 | T12.9 | A53.0 | E11 |
| 1 | C61 | D57.1 | J42 |
| 2 | I06.2 | D57.1 | J42 |
| ... | ... | ... | ... |

Data security

Of utmost importance in research data management is the protection of the data from accidental loss or unauthorized access. The integrity of the data depends on the security systems built into the data management enterprise. Such systems include hardware and software solutions such as firewalls, dedicated servers, secure networks, data encryption and user authentication through password and user name verification. But there are people solutions too, including assiduous training of research and information system staff on the need for protecting the integrity of the data. It is best if such training is reinforced through refresher courses annually or more frequently throughout the life of the project. Included in this training should be content about hardware and software issues, procedures for maintaining a secure data environment and the methods for preserving subject confidentiality and privacy. Privacy training should include cautioning against sharing of identifiable data with unauthorized persons or placing data on easily lost or stolen media such as portable drives or even laptop computers. Some hospital data systems in Africa may not have the highest quality antivirus software or may have antivirus software that is not updated after expiration of agreements or owing to intermittent internet connectivity. For these reasons scrupulous attention should be given to ensuring suitable antivirus protection for all research databases and other electronic data, and optimal data hygiene practices.

Data collection

If the database has been modelled appropriately, the next thing to consider is data collection. This is the step in the data management life-cycle where most mistakes are made, starting with poorly designed data collection forms. Great care should be taken in designing such forms whether they are intended to be used by research staff or as questionnaires to be completed by research subjects. Properly designed data collection forms are legible, at the reading level of the intended user and mapped to the design of the database as it has been modelled. These are three best practices that should be adhered to regardless of whether the data collection form is on paper or computer or other device such as a smart phone or tablet computer.

In many settings, collecting data on paper is a necessity, especially where there is no access to a reliable power source, which would be needed if a computer were to be used for data collection. Alternatives to

paper and computer are the smart phone and the tablet computers. These devices support access to wireless voice and data networks through 3G or 4G protocols, as well as myriad applications that are either available for download or can be programmed using only moderately advanced programming skills. There are many projects in Africa that have used smart phones or tablet computers for data collection. While these tools are quite useful for data collection, they offer little support for data management, which would require storing the data in a database and using database management software for editing, reporting and basic analytical functions.

Data entry

One should pay careful attention to the procedures used for entering data. Once collected, data need to be entered into a data management system, but if one is collecting these data using a computerized system data entry occurs simultaneously with data collection. Such equipment are a laptop or desktop computer, or a smart phone or a tablet computer, which would need to be connected to an electronic data management system. There are some special techniques one can use with these tools to reduce the possibility of data entry errors. “Range checking” requires a user to enter data that fall only within a pre-specified range, say body temperature ranging from 36 to 41 °C. Temperature values outside this range would be disallowed and the user might see an error message. With the “required field” approach the user enters the values for a given field or variable and is not be able to continue to another field until the first field is completed. The “logic check” indicates to the user that the values entered for two or more related fields or variables do not make sense, for example if the user enters a value of “2” for number of times pregnant and the sex as “male”. Logic checks can be handled with error messages showing discordance between values entered for these fields, but a more sophisticated approach is to disable an incompatible field, such the pregnant field for male patients. In some software this is accomplished by disabling the field on the display screen while in other software the incompatible field is not displayed.

Data management

Research data need to be evaluated for accuracy and completeness, stored and protected from access or use by unauthorized persons. This requires sophisticated infrastructure that, fortunately, is easily available and relatively inexpensive to maintain. First, one would need a data server, which will typically be a computer with a hard disk or a set of disks of sufficient capacity for data from the project or numerous projects. Such a server could be a mid-range desktop computer with as much hard disk space as one can afford, perhaps one to two terabytes or more if needed. Processor speed, graphics capacity and random-access memory (RAM) are not such important considerations as disk space if the server is intended primarily as a resource for storing data and providing users with access to the data for data management and analysis. Good quality data servers are widely available in the marketplace for a reasonable cost.

If one intends to analyse research data, a computer with substantial processing speed and RAM might be required, depending on the size of the database to be analysed and the complexity of the analyses. The best practice is to purchase the computer with as much speed and disk storage as you can afford. Most statistical analysis software loads a portion of a data set or the complete data set into memory, or “swaps” portions of the data set in and out of the memory using the hard disk as temporary storage. A computer intended to support statistical analysis will need to have more capacity than most of the off-the-shelf computers one can purchase; for analysis, and even local data management purposes, one should expect to acquire additional RAM or disk space.

Database management software

Tablet computers and smart phones support a wide array of applications that are ready-made or tailorable for collecting research data. But these technologies will require additional software for the types of data management and analytic tasks required in research. Such type of software are database management

systems (DBMS). Several excellent DBMS packages are available for relatively low cost. Programs such as Microsoft Access and FileMaker provide substantial capacity for handling very complex databases, such as those with many records or variable fields. They run in Microsoft Windows or Apple Macintosh OS environments, although Access will require installing a Windows emulator such as Parallels program to use with Apple computers, as it does not run natively in that environment. Both Access and FileMaker require substantial training to use them effectively.

Simpler and cheaper software options exist for data management. One well-known and venerable data management software package is Epi Info. This package is available free of charge from the US Centers for Disease Control and Prevention (<http://wwwn.cdc.gov/epiinfo/>). Epi Info is a public domain software that is usually used by public-health practitioners and researchers and as such is well suited to fieldwork. It is a comprehensive software suite, supporting data entry forms, logical data entry with error checking, graphics and analysis, as well as export of data for use by other analytic programs. It runs under Windows on even modestly equipped computers. It does not run on Macintosh OS unless they are equipped with a Windows emulator. One significant advantage of Epi Info over Access or FileMaker is its ease of use. With minimal training, one can set up a database with a full-feature data entry form in much shorter time than with the commercial packages. Epi Info is best suited to projects using questionnaires or other instruments where data are collected at one time rather than longitudinally.

REDCap is a free, web-based DBMS that was developed at Vanderbilt University under their Clinical Translational Science Award (www.project-redcap.org). Like Epi Info, REDCap supports a wide range of data management tasks, from design of data entry forms to export of data for analysis in formats appropriate to the most widely used statistical analysis software. REDCap also supports a small number of statistical and graphical procedures limited to descriptive statistics and frequency distributions. The ability to export data in a variety of formats is the important strength of REDCap. One can export comma-delimited (.csv) files for use in many other software packages, as well as program files for analysis programs such as R, SAS, SPSS and Stata. These program files access the exported .csv files to create data sets in the formats supported by these analytic packages.

Another advantage of REDCap over other DBMS software is its built-in support for a variety of study designs, including simple observational studies, longitudinal (prospective) studies, clinical trials and surveys. With REDCap one can set up a calendar that incorporates automatic prompts for the users on the forms required for a particular research subject's visit or, in the case of a survey, one can set up automatic mass emails to invite potential respondents to participate.

Of particular interest to research in Africa is REDCap's large global presence. It is being used by over 500 institutions in 48 countries, including Malawi, Nigeria, South Africa, Tanzania, Uganda, and Zimbabwe. There is a very large global support network with user groups, webinars and other online resources.

REDCap provides a highly secure environment for data management. Because the software and the data are situated on a server, typically on a secure network behind a firewall, confidentiality and privacy are better and more easily maintained than with any of the other DBMS mentioned here. REDCap is highly regarded for this feature. Because the REDCap software and database require a web server, including hardware and web services software, and a trained network administrator to install and maintain it, it could be out of the reach for institutions or projects that do not have such resources. It is important to keep in mind, though, that the skills needed to support REDCap are well within the reach of any individual who has some skills in web server administration.

Statistical analysis software

There are a number of proprietary statistical analysis software as well as free options. Well-known commercial packages such as SAS, SPSS and Stata require licenses for use and, depending on the licensing arrangements for a particular institution, licensing costs could be prohibitively high and require annual renewals. Some benefits of these packages are the support provided for state-of-the-art statistical procedures and access to an extensive user community from which to draw assistance on questions or problems. In addition, they run on personal computers or servers under all of the popular operating systems. One lower cost proprietary analysis package is JMP, which is available from the SAS Institute (www.jmp.com). JMP is a graphically-based analysis package that is excellent for students or others just starting out in statistics but has enough capability to handle sophisticated analytical tasks. JMP is unique in that it runs on not only the typical computing platforms but also iPad.

There are a number of free analysis programs of which the standout in terms of comprehensiveness and user support is R (<http://www.r-project.org/>). R is a complete statistical analysis and graphics environment that runs on Windows, Macintosh and Unix platforms. In addition to the main R program, there is a panoply of “packages” or software add-ins developed and tested by members of the R community. These are typically statistical programmers, statisticians and others who contribute programs in community interest, which is the best practice of the open source movement. Other free data analysis programs include Epi Info, OpenEpi, the biostatistics library at the MD Anderson Cancer Center, and WINPEPI, which is a collection of statistical programs for epidemiologic analysis.

Other software

A number of other software programs are indispensable in data management and analysis. These include PS (<http://biostat.mc.vanderbilt.edu/wiki/Main/PowerSampleSize>), a freely available, Windows-based, sample size and power calculator that is easy to learn to use. It is an excellent program for teaching sample size concepts to students. A another very useful program that is StatTransfer (<http://www.stattransfer.com/>), a commercial program for converting databases and data sets across 40 different file formats including SAS, SPSS, Stata, Excel and many others. StatTransfer uses a graphical interface, and is available for all operating system platforms including Windows, Mac OS-X and Linux.

Bibliographic reference software is very helpful when writing manuscripts, as it supports downloading of references from online resources such as PubMed and organizing them into a database. The automatic citation capability allows references to be added into the manuscript as they are cited during writing using a word processor and to be automatically added to a reference list at the end of the document. Reference Manager (<http://www.refman.com/>) and endnote (www.endnote.com) are two well-known commercial reference management programs. RefWorks (<http://www.refworks.com/>) is a free, online reference manager that is offered through university libraries that subscribe to the service. Table 4 provides a description of software resources that one will find useful in data management and analysis.

Table 4: Commonly used software packages for data management and analysis

| Function | Software | Features | | | | | |
|---------------------|-------------------|------------|-----------------|-------------------|----------|------------------------|-------------------------------------|
| | | Data entry | Data management | Report generation | Graphics | Operating system | Cost/licensing |
| Database management | FileMaker Pro | ++++ | ++++ | ++++ | +++ | Windows Mac | One time fee/perpetual license |
| | Microsoft Access | ++++ | ++++ | ++++ | +++ | Windows | One time fee/perpetual license |
| | REDCap | ++++ | ++++ | +++ | + | Web based | Free |
| | Excel | ++ | Not recommended | ++ | ++++ | Windows Mac | One time fee/perpetual license |
| Utilities | Endnote | ++++ | ++++ | ++++ | None | Windows Mac | Moderate/ perpetual |
| | Reference Manager | ++++ | ++++ | ++++ | None | Windows Mac | Moderate/ perpetual |
| | StatTransfer | No | ++ | No | None | Windows Unix Mac | Moderate/annual or perpetual option |
| Data analysis | RefWorks | ++++ | ++++ | ++++ | None | Web based | Free at subscribing institutions |
| | SAS | ++++ | +++ | ++ | ++++ | Windows Unix Mac | Expensive/annual |
| | SPSS | ++++ | +++ | ++ | ++++ | Windows Unix Mac | Expensive/annual |
| | Stata | ++++ | +++ | ++ | ++++ | Windows Unix Mac | Moderate/annual or perpetual option |

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Chapter 10

Clinical trials

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Chapter outline

1. Background
2. Clinical trials in the African setting
3. Existing collaborative resources and infrastructure for clinical trials in Africa
4. Best practices: meeting African needs while maintaining global standards

1. Background

The case for an interventional approach to cancer in Africa

In response to the looming global cancer pandemic, the World Health Organization (WHO) developed a comprehensive approach to cancer control comprising evidence-based strategies for its prevention, early detection, treatment and palliative care.⁽¹⁾ Research is critical to generate the evidence base for these strategies in developing countries. Effective and culturally relevant programmes must reflect current valid evidence from basic, epidemiological and clinical research. There is a wide disparity in research capacity between developing and developed countries, and many countries in Africa have extremely limited capacity. Epidemiological studies, crucial to identifying cancer risk factors and guiding public-health policy, comprise the majority of research effort in developing countries. Data from these studies support major initiatives aimed at risk reduction such as the Framework Convention on Tobacco Control. Basic research in cancer biology and molecular pathogenesis is also important given the fundamental differences in cancer etiology between developing and developed countries. Cancer caused by infections remains common in Africa, but there is a disproportionate focus on the continent on etiological factors seen in high-income countries.⁽²⁾

An interventional approach to the cancer burden in developing countries is urgently needed. Low-cost, effective interventions for early detection and treatment are available for several malignancies including childhood leukaemia and cervical, breast and testicular cancer but remain inaccessible for many people in developing countries. Advocates of rapid scaling up of cancer treatment such as the Global Task Force on Expanded Access to Cancer Care and Control in Developing Countries (GTF.CCC) call for immediate action in the face of existing needs, in addition to risk reduction and prevention efforts. Sceptics of that approach emphasize the scarcity of funds and perceived infrastructural obstacles to cancer treatment in poor countries, arguments resembling those cited a decade ago in debates about the feasibility of HIV treatment. In the case of HIV, the challenges were overcome by expanding access to antiretroviral therapy through innovative treatment models, introducing of new funding sources and concerted global action. These actions and the new treatment plans led to dramatic declines in HIV-related mortality. Experience with the HIV epidemic provides an important lesson that neither provision of health care nor prevention of disease can be neglected.⁽³⁾

An interventional approach relies on new and ongoing clinical research to ensure that care initiatives reflect current data and best practices in oncology that are appropriate for the region. While interventional research is increasing in developing countries and strides are being made in the areas of clinical trials, diagnostics and

cancer treatment technologies, more clinical research is still needed to better understand intervention capabilities and provide evidence for programme effectiveness.⁽²⁾

The basics of clinical trial design

Clinical trials are required for the successful development of effective and safe interventions. A clinical trial is a carefully designed, prospective medical study that attempts to answer a precisely defined set of questions with respect to the effects of a particular treatment. The results of a clinical trial, which are based on a limited sample of patients, are then used to make decisions about how a given patient population should be treated in the future. The majority of trials fall into one of three categories: phase I, phase II or phase III.

Prior to beginning the clinical stage (testing in humans) of research, a number of preclinical in vitro laboratory or in vivo animal studies are completed to obtain preliminary efficacy, toxicity and pharmacokinetic information. The main goal of the preclinical stage is to determine a product's safety profile.

Phase 0 trials are exploratory preclinical trials conducted early in Phase I, involving limited human exposure and without therapeutic or diagnostic intent. The purpose of the Phase 0 study is to assist in the “go versus no-go” decision-making process for a new therapy early in the development process using relevant human models instead of relying on sometimes inconsistent data from animal models. These early human studies help to confirm end-points such as the mechanism of action, pharmacology, bioavailability, pharmacodynamics and metabolic assessments. Phase 0 studies are generally designed for a small number of patients, usually 10 or fewer, for a limited duration and using a very low dose of the novel agent.

Phase I trials are the first studies conducted on humans after the completion of preclinical studies. The usual aims of a phase I studies are to establish the maximum tolerated dose for the new drug, identify the dose-limiting toxicity, determine the pharmacokinetic and pharmacodynamic profile of the drug, and document possible antitumour activity. Patients with advanced disease that is no longer amenable to established forms of treatment are often selected for phase I trials of anticancer drugs.

Phase II trials are carried out after the phase I assessment of a new agent but before large-scale, randomized phase III trials. Single-agent phase II trials assess the activity and toxicity of a new agent in a defined tumour type. The primary end-point for single-agent phase II trials is antitumour activity expressed in terms of response to therapy. Often the information provided by phase I and single-agent phase II trials is not sufficient to justify a large randomized phase III trial, particularly when a new agent is incorporated into a combined therapy. Feasibility trials are phase II trials that explore the therapeutic effect of a new agent or of an established active agent in combination with other drugs or other treatment modalities with the aim of justifying a subsequent large, randomized phase III trial.

After a drug has been determined to have activity in phase II trials, the next step is to determine its relative efficacy in a randomized phase III trial. Phase III trials compare the experience of a group of patients receiving a new treatment with a group of patients receiving the standard treatment or an untreated (placebo) control group. Patients are selected only if there is substantial uncertainty over the best treatment for their disease and are assigned to a treatment group by a random process. Randomization is the single most important technique to prevent selection bias, balancing the distribution of both known and unknown prognostic factors in the treatment groups so that a difference in outcome can reasonably be attributed to a difference in treatment effect.

With clinical trials becoming more and more complex, necessary quality assurance systems must be established to ensure that the trial is performed correctly and the data are generated in compliance with the standards of good clinical practice.⁽⁴⁾

Current international standards for trial design, ethics and regulation

Declaration of Helsinki

The importance of establishing a code of ethical principles to guide physicians and scientists in conducting human research was recognized in the aftermath of World War II. The Nuremberg Code, prepared in 1947, became the first document to set forth standards for human research. Subsequently, the World Medical Association adopted the Declaration of Helsinki in 1964, which emphasized the rights of participants in human research and clearly defined the requirements for fully informed consent.

International Conference on Harmonization

In 1990, the International Conference on Harmonization (ICH) was convened as a joint initiative of the health industry, academia and various ministries of health from Japan, the European Union and the United States. The mission of ICH was to discuss and define the minimum standards for the development and registration of investigational drugs and devices.

ICH's mission is to achieve global harmonization to ensure that safe, effective and high-quality medicines are developed and registered in the most resource-efficient manner. ICH guidelines cover the four categories of quality, efficacy, safety and multidisciplinary. Each category consists of numerous guidelines.

Good clinical research practice

The ICH efficacy guideline E6 or “good clinical practice (GCP)” guidelines are the accepted international ethical and scientific quality standard for the design, conduct, recording and reporting of trials that involve human participants. Compliance with GCP is intended to provide public assurance that the rights, safety and well-being of those participating in clinical trials are protected, and to ensure the integrity of clinical research data.⁽⁵⁾

2. Clinical trials in the African setting

Most clinical trials conducted in Africa have been part of the global effort to develop interventions against the “big three” diseases of HIV infection, tuberculosis and malaria. Initially, these trials were typically led by non-African sponsors and investigators, whose common approach was to do the minimum site development required to perform a specific trial. External contract research organizations (CROs) provided the necessary expertise for conducting the trials. The CROs put African scientists under intense pressure to meet GCP guidelines only to disappear after recruiting the necessary number of patients, leaving little behind in the way of sustainable infrastructure or human expertise and impeding local ownership of the research agenda. Furthermore, the clinical trial centres that were developed in Africa were generally strongly linked to northern partners, and local scientists were not empowered to engage in an equitable and effective way with industry or other partners involved in product development.⁽⁶⁾

Systematic reviews of clinical trials in Africa substantiate these observations. For example, a South African group reviewed all randomized controlled trials (RCTs) of HIV/AIDS in Africa through 2008 and found that most principal investigators were based in the USA with only a few in Africa. Most trials were funded by several organizations with the most of the funding originating from United States governmental and nongovernmental agencies followed by United Kingdom governmental and nongovernmental agencies. Few trials were funded by African organizations, particularly governments. In sum, it was clear that non-African researchers generally conducted research in Africa on behalf of external agencies in collaboration with African researchers. While collaboration can encourage the transfer of skills to African researchers and ensure that the interests of the host country are considered, there is need for capacity development of local

investigators in clinical research with the ultimate aim of ensuring that the research agenda of the African continent is driven from within.⁽⁷⁾

There has also been an effort to empirically evaluate the major ethical controversies associated with the growth of clinical research in developing countries. A systematic review of RCTs in sub-Saharan Africa aimed to quantitatively assess the relationship among international collaboration, funding and local relevance, given the concern that research collaboration may serve the interests of foreign collaborators more than those of the host countries. The study found that research relevance to Africa was not adversely affected by collaboration with non-African investigators.

Another study investigated the clinical standards generally applied in trials conducted in sub-Saharan Africa, given the intense debate over the minimum standard of care required for trial participants in resource-poor settings. This debate was ignited in the 1990s when placebo-controlled trials of less intensive antiretroviral regimens were conducted on HIV-positive women after trials had already established that an intensive antiretroviral course reduces the risk of vertical HIV transmission. Some people argued that research participants must receive the “best proven” treatment regardless of context, while others argued that trial design must be sensitive to local levels of care in order to be relevant to the local population. A systematic review of all RCTs of HIV and tuberculosis treatment, and malaria prophylaxis conducted in sub-Saharan Africa from 1998 to 2003 found that only in 16% of the trials did both the intervention and control groups receive therapies that met “best current” standard of care guidelines. Only 1 of the 34 HIV trials provided an antiretroviral treatment that conformed to guidelines, whereas all patients in the tuberculosis trials were treated according to clinical guidelines. Although the malaria prevention trials tested interventions that met the guidelines, most did not provide active prophylaxis to the control groups.⁽⁸⁾

There are signs that the clinical trial landscape in Africa is changing. For example, in recognition of the need to strengthen clinical trial capacity, the African-led Malaria Clinical Trials Alliance (MCTA) was launched in 2006 with support from the Bill and Melinda Gates Foundation. MCTA, a programme of the INDEPTH Network of demographic surveillance sites, had two objectives:

- (a) To facilitate timely development of a network of centres in Africa with the capacity to conduct GCP-compliant trials of malaria vaccines and drugs.
- (b) To support and mentor the centres as they progressed toward becoming self-sustaining clinical research centres.

In three years, MCTA enabled 13 centres to perform GCP-compliant trials, providing laboratory and facility refurbishment, arranging workshops on GCP, providing malaria diagnosis, and organizing training on strategic management and media use, and for accreditation examinations of the Association of Clinical Research Professionals (ACRP). The MCTA experience shows that research centres can be brought up to GCP compliance in a reasonable time scale, although the costs are substantial. There is a need for support of other centres to meet the growing demand for clinical trial capacity. Notably, the centres involved in a large phase III malaria vaccine trial were more successful on average, indicating that capacity development may be best carried out in the context of preparation for and involvement in specific trials.⁽⁶⁾

Examples of cancer trials in Africa

Some of the first oncology trials in Africa were in AIDS-related malignancy, an important etiology of cancer in the developing world. While the incidence of opportunistic infection and AIDS-related malignancy have declined in the industrialized world since the introduction of highly active antiretroviral therapy (HAART), the incidence of Kaposi sarcoma and, in particular, non-Hodgkin lymphoma, has increased in the developing world. Furthermore, other viral-induced malignancies such as cervical cancer, hepatocellular carcinoma and Burkitt lymphoma have become common causes of morbidity and mortality. With the increasing burden of

these neoplasms in Africa, clinicians recognized that in addition to becoming skilled in their management, there was a critical need to develop research capacity to study these diseases and identify the strategies for their prevention. With this backdrop, a team of investigators based in the United States, Uganda and Kenya formed a research collaboration in 1996 dedicated to AIDS malignancy and supported by the National Cancer Institute (NCI).

The research priorities identified by this team for AIDS and other viral-associated malignancies included development of testable prevention strategies and pragmatic therapeutic interventions. With the increasing knowledge that much neoplastic disease in this setting is transmissible and theoretically preventable, large-scale prevention trials are required to develop prevention strategies. Examples include the use of antivirals to prevent Kaposi sarcoma, hepatitis B vaccines to prevent hepatocellular carcinoma and human papilloma virus vaccines to prevent cervical cancer. Equally important is the development of therapies that match the supportive care capabilities of the local community, which requires pragmatic clinical trials. For example, the need for effective non-myelosuppressive therapy for AIDS-related malignancies in resource-poor settings cannot be overstated. Transfusion support is limited and the risk of neutropenic infection is high and likely fatal. Studies evaluating the best way to provide symptom control and palliative care, including hospice services, were identified as a research priority.⁽⁹⁾

With these objectives, an international team developed a platform of clinical research trials with a pragmatic design. They pursued a feasibility trial of dose-modified oral combination chemotherapy for first-line treatment of AIDS-related non-Hodgkin's lymphoma. This was the first study of its kind on the African continent. Each of the drugs in the oral regimen was listed on the WHO essential antineoplastic drug formulary with the exception of etoposide. Other protocols developed by the team included a trial of the non-myelosuppressive regimen bryostatins plus vincristine for second-line therapy in AIDS-related non-Hodgkin's lymphoma and a feasibility trial of the protease inhibitor indinavir in endemic (HIV-negative) Kaposi sarcoma. The team pointed to the formal training of investigators and research personnel on clinical problems faced by East African practitioners as key to the success of their efforts.⁽⁹⁾

Cancers previously thought to be problems almost exclusively in the developed countries, such as breast cancer, are now recognized to be on the rise in developing countries. The significant disparity in mortality rates between global populations for several cancers has garnered research interest in recent years. For example, epidemiologic and genetic studies of breast cancer in African women living in industrialized western countries demonstrate that women of African descent are more likely to develop breast cancer at a younger age and with a more aggressive genotype and corresponding phenotype than women of European descent.⁽¹⁰⁾ These data provided the impetus for a group of collaborators from the United States and Nigeria to build an infrastructure for conducting early phase clinical trials in Nigeria, with the ultimate goal of developing targeted therapy for the aggressive breast cancers that disproportionately affect African women. The initial studies planned by the group included a phase II trial of neoadjuvant Xeloda in locally advanced breast cancer and a phase I trial of concomitant chemoradiotherapy with Xeloda in patients with advanced breast cancer.⁽¹¹⁾

3. Existing collaborative resources and infrastructure for clinical trials in Africa

The effort to expand cancer research and clinical trials in Africa will benefit from using existing resources and infrastructure. Major programmes relevant to this effort include the European and Developing Countries Clinical Trials Partnership (EDCTP), the Pan African Clinical Trials Registry, and the African Organization for Research and Training in Cancer (AORTIC).

European and Developing Countries Clinical Trials Partnership

The European and Developing Countries Clinical Trials Partnership (EDCTP) was created in 2003 by the European Parliament to establish and strengthen research capacity in developing countries. EDCTP is a

partnership of 14 European Union (EU) member states, Norway, Switzerland and developing countries in sub-Saharan Africa, formed to develop new clinical trial interventions to fight HIV/AIDS, malaria and tuberculosis in the sub-Saharan region. EDCTP responsibilities include a mandate to fund phases II and III clinical trials; support research capacity building, advocacy and information management; and promote North–South and South–South (or intra sub-Saharan Africa), networking. EDCTP strives to achieve true partnership by offering full support only to African scientists, promoting African ownership of projects and receiving backing and advice from African committees of scientists and regional health representatives. Through North–South networking, EDCTP aims to strengthen research through graduate study programmes, technology transfer, hands-on research training in the field and scientific exchange in the context of actual research programmes.⁽¹²⁾

EDCTP faced major challenges in its first few years leading to a slow start, but it subsequently developed into a formidable funding force for medical and scientific research and development (R&D) and capacity building in sub-Saharan Africa. The investment of 255 million euros by EDCTP has funded 141 projects involving 126 institutions in 28 sub-Saharan African countries and 43 European institutions. Proponents call for synergistic alignment of EDCTP with other funding agencies involved in supporting R&D in Africa, such as the Wellcome Trust and the Global Fund, and brokerage with national governments in Africa to ensure that capacity building is sustained over time. Development of effective capacity in all African countries will allow extending of research and development to the growing problem of noncommunicable diseases, including cancer (13).

Pan African Clinical Trials Registry

Prospective trial registration was needed as a means to reduce the effects of selective reporting and publication bias, which is the tendency to prefer publishing positive and significant trial results, leading to a skewed presentation of facts in public records. In 2004, the WHO was called upon to establish a registry network to provide a single access point to identify trials. In 2007, the International Committee of Medical Journal Editors (ICMJE) made registration a minimum standard for publication in ICMJE journals. The Pan African Clinical Trials Registry was established, initially as the AIDS, TB and Malaria Clinical Trials Registry, but in 2009 it expanded to encompass all diseases throughout Africa, becoming the only member of the Network of WHO Primary Registers in Africa. In addition to its primary objective of registering clinical trials on the continent, the registry aims to increase transparency and self-sufficiency amongst national regulatory bodies to encourage clinical trial monitoring.⁽¹⁴⁾

The African Organization for Research and Training in Cancer

The African Organization for Research and Training in Cancer (AORTIC) is a non-profit organization dedicated to cancer control and palliation in Africa. Among its key objectives is to further research relating to cancer prevalent in Africa. Originally founded in 1982, AORTIC held three scientific meetings in the 1980s that produced noteworthy clinical research. Such early work includes a randomized study comparing doxorubicin and epirubicin in primary liver cancer in five African countries, a study on the early detection of cervical carcinoma in Zimbabwe, a study of epirubicin versus radiotherapy for nasopharyngeal carcinoma in Kenya, Tanzania and Zimbabwe, and a study of radiotherapy versus chemotherapy for AIDS-related Kaposi sarcoma. The organization subsequently became dormant for a variety of reasons but was reactivated in 2000 and has since succeeded in putting cancer on the public-health agenda in many African countries. AORTIC conferences have been held every two years since 2003, attracting steadily increasing numbers of participants and fostering collaboration to build research training capacity and establish clinical research, among other initiatives.⁽¹⁵⁾

4. Best practices: meeting African needs while maintaining global standards

The ICH-GCP guidelines are widely accepted as the global quality standard for clinical research, though not without reservations. The mandates of GCP have added a dimension of complexity to clinical research that, while strengthening the ethical and scientific integrity of data, may lead to conflicts with cultural, political and socioeconomic realities and values. Certain minimum standards for conduct of clinical trials are defined, however, such as ethical and regulatory oversight, informed consent, protection of participants against undue inducement, and access of participants to good care at the end of the research project.⁽¹⁶⁾

Conducting vital research in resource-poor settings is often fraught with practical difficulties, and so sound ethical frameworks are vital to safeguard against possible exploitation of research participants. Many communities in Africa are highly vulnerable and may not be in a position to influence any decisions with regard to their own participation in trials.

Clinical trials are an essential part of the development of a new drug or device. Such studies are often an expensive process. An increasing proportion of clinical trials are now taking place in developing countries. It is alleged that in the past some of the studies may not have been conducted to the highest standards. This does not mean that all clinical trials in developing countries are unethical, but may involve more complex issues than research conducted in more resource-rich settings for a number of reasons:

- (a) Health care in Europe and the United States is of a high standard and a study participant in a developed country would have less to gain as well as more to lose from possible side effects tested in a trial. In other words personal cost-benefit balance for such a person would be different from that of a participant in Africa.
- (b) Because the participants in Africa are often not already on a specific drug, the sponsoring company does not have the expense of providing the standard treatment to the control group.
- (c) It is considered unethical to use a placebo when there is an existing effective standard treatment. If the standard treatment is not routinely available in the developing country, it may be regarded acceptable to use a placebo only instead of active treatment.
- (d) The rigorous standards that require the consent forms to contain all available information can pose a daunting and overwhelming challenge to someone with limited education. The use of multiple languages is a feature in many parts of Africa and consent should be available in the language of the participant; that means language that is easily understood by a lay person in the community where the study will be performed.

Ethics committees and institutional review boards

A key requirement of GCP compliance is independent, strong ethical and regulatory oversight of clinical trials to ensure the safety of research subjects and scientific integrity of clinical data. GCP defines the ethics committee main responsibility as to "... safeguard the rights, safety, and well-being of all trial subjects".

Independent ethics committees (IECs) or institutional review boards (IRBs) are responsible for reviewing and approving trial documentation such as the protocol, investigator brochure, financial information, investigator CV, and informed consent form and any other documentation given to the participant before the start of the trial activities. ICH GCP stipulate that at a minimum an ethics committee is to be made up of:

- (a) at least five members;
- (b) at least one member whose primary area of interest is in a non-scientific area;
- (c) at least one member who is independent of the institution or trial site.

In multinational trials all partner institutions should independently apply for approval by the local IRB.

Informed consent and assent

A major requirement of GCP compliance is informed consent, which conventionally serves as the cornerstone for protection of study participants from exploitation.

By consulting with the community, researchers often gain insight about whether the research question is relevant and responsive to the health needs of the community. In addition, community consultation can improve the informed consent process and resolve problems that arise in this process associated with the use of difficult or unfamiliar concepts. Community advisory boards (CABs) are useful to understand the local community and to facilitate communication between researchers and participants. The advisory board is often particularly important in the planning phase of large community-based studies.

According to ICH GCP, the investigator should comply with the applicable regulatory requirements and should adhere to GCP and to these ethical principles:

- (a) Prior to enrolling any patients, the informed consent form needs to have written, favourable approval from the IEC.
- (b) The informed consent form should be revised and approved by the IEC whenever important new information becomes available that may be relevant to the subject's participation.
- (c) The participant must not be coerced or unduly influenced by the investigator or any trial staff to participate or to continue to participate in a trial.
- (d) The informed consent form should contain no language that appears to waive any legal rights.
- (e) The participant must be fully informed on all pertinent aspects of the trial, including the written favourable opinion by the IRB or IEC.
- (f) The language used in consent form should be as nontechnical as practical and should be understandable to the subject.
- (g) The subject should be provided with ample time and opportunity to request further information about the trial, and all questions should be suitably answered.
- (h) Prior to a subject's participation in the trial, the informed consent form should be signed and personally dated by the subject and by the person who conducted the informed consent discussion.
- (i) The subject should receive a copy of the signed and dated informed consent form.
- (j) An assent form is sometimes required in cases involving people with diminished understanding such as minors, or patients with severe dementia.
- (k) Informed consent in emergency situations, for example when a subject is unable to consent personally owing to their decreased level of consciousness, may be problematic. In studies performed in such highly vulnerable populations, IRB approval of the consent process should include detailed methodology.

Educated health personnel and staff

Although the investigator takes full responsibility for the study conducted at his or her site, there is a requirement to still demonstrate that the entire research team is adequately qualified to perform the task at hand. Evidence of such qualifications needs to be available through an up-to-date curriculum vitae or other relevant documentation. Each member of the research team needs to be aware of his or her trial-related duties and functions. The investigator should maintain a list of appropriately qualified persons with significant delegated trial-related duties. In some countries, it is a requirement to attend regular GCP courses. Numerous GCP courses are available online.

Reliable reporting of adverse and serious adverse events

An adverse event (AE) is any untoward medical occurrence affecting a study participant who received an investigational product and which does not necessarily have a causal relationship with the treatment. Adverse events are rated by the investigator for causal relationship, intensity, action taken and start and stop dates. An adverse event is considered as serious adverse event or SAE if it fulfils any of the criteria below and should be reported to regulatory authorities, the sponsor and IEC within 24 hours. A serious adverse event is defined as an untoward medical occurrence that at any dose:

- (a) results in death;
- (b) is life-threatening;
- (c) requires inpatient hospitalization or prolongation of existing hospitalization;
- (d) results in persistent or significant disability or incapacity;
- (e) is a congenital anomaly or birth defect.

Clinical data management

Data management is an integral part of the clinical trial life-cycle and covers all the aspects related to processing of data. This includes the entry, verification, validation and quality control of data gathered during a clinical trial. Numerous international guidelines exist governing clinical data management, including:

- (a) GCDMP (Good Clinical Data Management Practices) is a detailed guideline providing comprehensive advice on the setting up and management of a high-quality data management department. A good data management department should have standard operating procedures (SOPs) governing all major operations such as IT security, access and maintenance; database build and validation; and case report forms (CRF) receipt, entry, storage and archiving.
- (b) 21 CFR Part 11 is a regulation from the United States that has been adopted internationally as the gold standard for managing and maintaining electronic records. It defines the criteria under which electronic records and electronic signatures are considered to be trustworthy, reliable and equivalent to paper records.
- (c) The clinical Data Interchange Standards Consortium (CDISC) is a method for recording and reporting of clinical trial data through a set of standards used in the design of databases.

Post-marketing studies and pharmacovigilance

Phase IV trials are also known as post-marketing surveillance studies and are conducted on a product after it receives marketing registration, to either expand the safety surveillance (pharmacovigilance) of the product or to expand its technical data. Safety surveillance is designed to detect any rare or long-term adverse effects over a much larger patient population and longer time period than was possible during the phases I–III clinical trials. Expanding the technical data after registration of a new product is done for various reasons, including as a regulatory authority requirement, for marketing reasons in which case it is conducted by the sponsor, or to expand the drug dossier, for example its interactions, the populations on which it has been tried, or its performance compared with a comparator.

Access to treatment

The issue of the availability of the drug to the trial participants when the trial ends is much debated and many would consider a trial unethical if it does not provide follow-up treatment. The Helsinki Declaration states that "... medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research" and that "At the conclusion of the

study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study”.

The current number of trained and qualified principal investigators in clinical trials and support staff is still small in Africa and in dire need for expansion, which can be addressed by the provision of long-term training at graduate, postgraduate and professional levels. This is an expensive but necessary venture and must be addressed by all interested partners on a sustainable basis. Those involved in building a sustainable, functional clinical research platform in Africa should bring on board African governments, the private sector, bilateral and multilateral agencies and philanthropic foundations. All these partners are stakeholders in the activities at the research centres in different capacities at different times. Their support will succeed if it is based on trust and guided by professionals who understand the dynamics of clinical research in resource-poor settings.⁽⁶⁾

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SECTION III: COMMUNICATING RESEARCH

Chapter 11

Research advocacy: principles and practices

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Chapter outline

1. Research advocacy nuts and bolts
2. Framework for research advocacy: an advocate's perspective on principles to practices
3. Case study—How sociocultural factors act as barriers to breast cancer care in black South Africa: lessons for Africa
4. Conclusion

1. Research advocacy nuts and bolts

According to the World Health Organization (WHO), advocacy is the “effort to influence people, primarily decision-makers, to create change, which in the context of cancer control results in comprehensive policies and effective programme implementation, through various forms of persuasive communication”.⁽¹⁾ Research advocacy is one of six types of advocacy, with the others as political, education, community outreach, support, and fundraising advocacy.⁽²⁾ Research advocacy in cancer aims to ensure that research is tailored to the priorities of cancer patients.⁽²⁾ The activities of research advocates include:

- (a) Driving research questions by being part of a research team that develops grants and research protocols.
- (b) Protecting research participants by serving on the grant review panels and institutional review boards (IRBs) reviewing research protocols.
- (c) Assisting in the recruitment and retention of research participants in biomedical research.
- (d) Assisting in the interpretation of study results for patient or public use.
- (e) Promoting the dissemination of research results to patients and the general public.

Although cancer advocacy is in its infancy in Africa, research advocacy is an area of active practice in on the continent. In a review of African advocacy organizations, Odedina, Rodrigues and Raja⁽³⁾ found that about 72% of participating organizations focused on research advocacy. For cancer, this is a big step in the right direction to foster appropriate research that will address the needs of cancer patients. However, much work still needs to be done especially with respect to protection of research participants and their recruitment and retention, and dissemination of research results.

2. Framework for research advocacy: an advocate's perspective on the principles and practices

As the research system in Africa is developing and gaining strength, it presents an opportune moment for research advocacy to be an embedded component in continental research structures. The framework for research advocacy in Africa can be developed drawing from the experience of and infrastructure for research advocacy in developed countries such as the United States. However, it is expected that the modes of research advocacy in African countries will differ from those in developed countries and will be aligned with

the countries' and regional norms, cultures, religions, languages and support processes. Nevertheless, the essential advocacy framework for Africa can be built on the principles that contribute to the success and influence of patient and research advocacy in the USA.

Basic principles of research advocacy: making the case

Patient advocacy is not a new concept in Africa but it is in its early stages of development, with groups dotting the health landscape such as the Breast Cancer Association of Nigeria, Tanzania 50 Plus Campaign, and People Living with Cancer. Such groups and the growing continental research capacity are bolstered through the work of organizations like the African Organization for Research and Training in Cancer (AORTIC). Research advocacy is critical to cancer prevention and control as it will strengthen the research process, change the way researchers see patients and consider patient needs, and keep patients at the centre of research thinking and conduct. This is because advocates:

- (a) Put faces on the disease. Many researchers will have encountered only the most ill patients and at their very worst.
- (b) Give voice to all patients and survivors and increase awareness of cancer issues and of clinical trials. Patient voices are unique, experience based and indispensable.
- (c) Ask questions specific to the experience of living with or caring for someone with cancer.
- (d) Create a sense of urgency by their very presence.
- (e) Form mutually respectful and beneficial partnerships and relationships with researchers.
- (f) Provide hope to cancer patients and their families.

Without a doubt, research advocacy results in research that is more focused on issues important to patients, more patient friendly and more likely to recruit informed participants, thereby increasing the prospect of benefit to patients.

The framework for research advocacy is based on a partnership between advocates and researchers, thus, research advocacy should be seen as critical for the most patient-centred, accruable research. However, research advocacy is not easy, is not for those easily discouraged and requires significant investments of time and effort. It also requires dedicated advocates, a supportive advocacy network and research system, training and education for advocates and researchers, a state of mutual respect and acceptance between advocates and researchers, and private and public sector investment and support. To promote the growth and influence of a viable Afrocentric research advocate network, the framework for research advocacy must be country specific and African led with the support and guidance from countries and regions with model frameworks.

Associated practices: working within a framework

A pipeline of volunteers

To have a continuous pool of effective research advocates, a pipeline of willing and able volunteers must emerge. Research advocates can come from any walk of life with many of them start as support, community outreach, education, political or fund-raising advocates. Whatever their route of entry into advocacy, they are everyday citizens such as:

- (a) patients, survivors, family members and caregivers;
- (b) curious and willing learners with or without a medical background;
- (c) community liaisons with the ability to read, write or speak in the language of the populations represented or served;
- (d) members of health advocacy groups or other activist efforts;

- (e) scientists and clinicians personally affected by cancer;
- (f) other interested individuals with the time for and commitment to research advocacy.

Continuous training and education

Many people are drawn to advocacy through personal or family experience with cancer. They get into advocacy without formal advocacy experience. Thus, training and education are very important to prepare them for research advocacy. Training can occur through independent study, informal education through interaction with other advocates, use of online resources, formal advocacy training programmes, attendance and participation at scientific meetings, networking with other advocates, and experiential training under an experienced advocate. A combination of both formal and informal training techniques is best to adequately prepare for research advocacy.

Opportunities to improve skills and serve

Once trained, research advocates can grow in proficiency and influence, providing patient perspectives and keeping the focus firmly on patients. They will serve on ethics committees, panels for review of the research concept and protocol, research teams, grant funding panels, and other research-focused groups. While their opportunities and responsibilities may vary across the continent, there will always be advocacy opportunities if there are prepared, committed advocates willing to share their collective experiences, to be persistent but concise in providing patients' point of view, to demonstrate deep concern and passion, and to build relationships rather than mark territory. Research advocates must always stay focused on ensuring optimal benefits and outcomes for patients.

Patient-centred focus

In focusing on patient benefits and outcomes, research advocates concentrate on specific types of issues and often frame comments and concerns as questions. For example, they might ask:

- (a) What will this research mean in terms of care, quality of life or survival?
- (b) Could the results of the research change the practice or add to treatment options?
- (c) Does the trial include provisions to overcome possible barriers to patient participation such as distance from the trial site, frequency of visits, incidental costs and language- and culture-related issues?
- (d) Who will supply the experimental drugs?
- (e) Will there be a cost to trial participants?
- (f) Will the drug be easy to take or administer outside of the clinic or hospital?
- (g) Will trial participants be able to work or take care of home responsibilities if they are involved in the trial?
- (h) Who and what groups, documents or procedures will protect the interests and safety of trial participants?

No one is better positioned to ask these questions or has more at stake than patients and their advocates.

Reality check: assessing research advocacy in Africa

Evaluating feasibility and achievements

The formation and first-year efforts of the African Cancer Advocates Consortium (ACAC) answer the question of whether establishing a viable African advocacy network is possible. ACAC was formed with 51 charter

members after the International workshop on cancer advocacy for African countries held during the 2011 AORTIC conference. In its first year, ACAC members have remained engaged, working on several initiatives. For example, they were instrumental in providing case studies for the *Cancer advocacy training toolkit for Africa* published by AORTIC, the African Oxford Cancer Foundation (AfrOx), the European Society for Medical Oncology and the Union for International Cancer Control.⁽³⁾ In addition, the ACAC leadership proactively alerts African advocates about advocacy education and training opportunities. ACAC is the beginning of a robust network, with regional and subspecialty representation, including of research advocacy. In a message to the “toolkit” users, David Kerr, founder and trustee at AfrOx, noted, that “One of the most important ways we feel we can help to reduce the burden of cancer in Africa is to work with African cancer advocacy organizations to help educate and advocate about cancer in their countries”.⁽⁴⁾

Research advocacy is both feasible and doable: the existence of active advocacy groups, AORTIC support and workshops that provide training across advocacy subspecialties, the regionally and subspecialty diverse ACAC model, and the “toolkit” serve as early evidence.

Addressing urgent needs

Among the most urgent needs in developing sustainable and robust research advocacy in Africa are:

- (a) Public awareness efforts that put cancer on the priority list of health issues in Africa.
- (b) A research structure that supports and embeds research advocacy as a core value-adding component.
- (c) Active recruitment and development of a core and pipeline of interested patients and other activists.
- (d) Ongoing training programmes built, in part, through collaboration and shared interests among advocacy groups across the continent and others from other regions of the world.
- (e) Global partnerships among advocates, researchers and clinicians.

3. Case study: How sociocultural factors act as barriers to breast cancer care in black South Africa: lessons for Africa

Introduction

Breast cancer is the most commonly diagnosed cancer and the leading cause of cancer death among women in southern Africa, with 9000 cases and 4500 deaths in 2008.⁽⁵⁾ The Dakar Declaration issued by AORTIC in 2011 captures the grim reality of the rising burden of cancer on the African continent.⁽⁶⁾ Concerted efforts are needed to implement cancer control strategies that are appropriate to the African sociocultural and material resource contexts. To be effective and sustainable, all interventions must be based on research knowledge and be conducted with the full participation of and in collaboration with African cancer patients and lay grassroots cancer organizations. The South African case reported here is an example of the role of patient-driven breast cancer research advocacy.

The case for patient-driven research: breast cancer case study

In a study entitled “Does that make me a woman?: Breast cancer, mastectomy and breast reconstruction decisions among sexual minority women”, Rubin and Tanenbaum⁽⁷⁾ discuss the sexist and heterosexist assumptions often embedded in the medical management of breast cancer and of mastectomy in particular. Their study addresses the three pertinent issues that BreastSens’ patient advocacy work centres on: (a) identifying the key determinants of why black indigent women in Soweto present with late advanced breast cancer disease at first consultation; (b) establishing who the primary decision-maker influencing a patient’s decision to have or not to have a mastectomy is, and (c) weighing the impact of sociocultural factors and paternalistic medical practices on women’s treatment-seeking behaviour.

BreastSens is a breast cancer advocacy nongovernmental organization devoted to promoting the voice of indigent breast cancer patients in the Soweto Township of Johannesburg. The organization undertook three group conversations with Soweto women in its service network to learn about their lived experiences of breast cancer associated breast loss. These conversations were conducted within a sociocultural context in which women's body frailties are highly stigmatized and not spoken of. Ten women between the ages of 26 and 46 participated in informal hour-long sessions during which they shared narratives on the theme "Breast cancer in Africa: do my breasts make me a woman?—threatened marriage and reproductive chances".

Though many indigent African women live in urban settings, native sociocultural belief systems still carry a lot of weight in daily life, including how women manage their health-care needs.

Belief in sorcery and witchcraft is deeply rooted and is not uncommon among people who are well educated as well as those who are poor. This seemingly dualistic belief system is visible in peoples' health-seeking behaviors, whereby western biomedicine and modern hospitals and clinics are popular and are widely utilized alongside the services of traditional healers. For the most part, people are able to manage the coexistence of what are essentially logically inconsistent religious traditions.^(8,9)

Understood within the African sociocultural setting and within the framework depicted in the words of feminist Nombulelo Gasa's comment about African women's bodies being highly contested within African societies, it becomes pertinent that breast cancer awareness campaigns and disease management or care interventions be framed differently from campaigns in industrialized countries. Our premise is that disease control efforts undertaken in South Africa and the continent of Africa need to be culturally appropriate to be successful. African women comprise the largest population group in South Africa at 64.2% of the total population.

Beauty and physical appearance considerations often trump health-care needs among women in the 20–35 age group. Marriage ability is key consideration among this age group, and the most frequently asked question in lay counselling sessions is, "Who is going to marry me without a breast", as 29-year-old Zoleka asked. It is very difficult to counsel a young woman whose main reason to grieve is loss of a future as bride, wife and mother, especially within the patriarchal African cultural context in which the ability to reproduce defines both womanhood and manhood. A man is a real man if he can sire offspring. By implication, a good man must find a good woman to bear him offspring and ensure the continuation of the family name.

Leclerc-Madlala et al.⁽¹⁰⁾ aptly depict how a woman's position and place are socioculturally defined within traditional African societies, including South Africa:

Still today women are very aware of cultural prescriptions to show respect by deferring to husbands and in-laws. Full acceptance within a woman's patrilineal home was only complete with the birth of her first born child, and especially when that child was a boy. From then on, culture dictated that a woman's term of address within the home would no longer be a term that translated into 'young wife', but henceforth a term that translated into 'mother-of-so-and-so'. As a mother of a child of a particular home and lineage, a woman was then more fully incorporated and accepted into her husband's family. These prescriptions continue to inform ways of thinking about marriage, motherhood and the role of fertility and children in society.

Pink-ribbon breast cancer messaging campaigns inspired by western culture do not recognize or incorporate the critical aspect of the indigent African woman's lived experience of deference to external male authority in matters pertaining to fertility and reproduction. Breasts within the traditional African sociocultural context are not sexual objects but are prized as a source of naturally wholesome food for offspring. One participant in the Soweto narratives explained her breast loss trauma of in terms of this cultural reference point: "Everybody in my neighbourhood used to call me 'Nyanya', like nursing babies affectionately call their

mothers' milk breasts". Dealing with the loss of a breast to cancer is, therefore, complicated for these women, especially the 17 million of them who live in the country's rural areas. For rural women, breast loss is not just a private and personal issue, it also affects their extended family networks. A young maiden's breast loss is potentially patrilineal loss for her father or maternal uncles, who are the traditional recipients of the "lobola" paid for her hand in marriage. Leclerc-Madlala et al. ⁽¹⁰⁾ explain the sociocultural value of patriliney with bride wealth as follows:

Marriage is legitimised in all these societies with the transfer of bride wealth from the husband's family to the wife's family, which traditionally takes the form of cattle. With this transfer a man and his family obtain considerable jural rights over his wife and children. Children born to a union were and are considered to be children of the father, and descent is traced through males. While various historic and modern pressures continue to undermine these traditional social arrangements, the combination system of polygyny, patrilocality and patriliney with bride wealth continues to have important repercussions and influences on the nature of marital relations and social relations more generally (p 15).

The intricacies of breast cancer and gender positioning within Africa are perhaps best captured by Nosipho's case. She was a 36-year-old mother of three, who was pregnant with her fourth child when she was diagnosed with breast cancer in December 2010. Nosipho was in her first trimester of pregnancy and her breast cancer diagnosis had direct implications for the unborn child. The doctor informed her of her illness, that her cancer was hormone receptor positive, which meant she faced a high risk of rapid disease growth and systemic spread. An elective pregnancy termination was recommended to maximize the efficacy of her chemotherapy treatment. Nosipho's mother-in-law was a recently retired nurse practitioner who had herself completed treatment for breast cancer, including a mastectomy, six months before the younger woman was diagnosed. The narrative of Nosipho and her mother-in-law is a clear example of the duality of belief systems that Leclerc-Madlala et al. ⁽¹⁰⁾ outlined in relation to African women's medical treatment behaviours. Despite her education, long career as an accomplished nurse practitioner, her recent mastectomy and systemic treatment, the mother-in-law viewed Nosipho's diagnosis and recommended termination of pregnancy as evidence of sorcery and the wrath of ancestors visited upon her as the matriarch of the family. She was convinced that she and her family were being punished and that the rage of her forebears was being manifested through an attack on her breasts, the organ of nurturance, then by a direct attack on the pregnancy (and the loss of a young life still in utero) and the breast of her young daughter-in-law (who was still in the prime of her reproductive years).

Leclerc-Madlala et al. ⁽¹⁰⁾ add that "As a daughter-in-law (Nosipho is) subject to numerous prescriptions for demonstrating 'respect' that define the way she (is) expected to interact with and be subordinate to members of her husband's family..." It is this deference that Nosipho's mother-in-law called for when she asked the young bride to participate in a family cleansing ritual and sacrificial offering ceremony to appease the wrath of the ancestors before attending to her impending pregnancy termination that was recommended by western biomedical practitioners. As far as the older woman was concerned, the family's combined maternal sphere was under attack, as manifested through her breast cancer and accompanying breast loss, the loss of an unborn child (a grandson, she insisted) and the daughter-in-law's subsequent diagnosis and indicated mastectomy.

It is difficult to appreciate the immense psychological trauma both women endured. Working with the younger woman brought squarely into focus the complex individual, familial and sociocultural challenges faced by women who inhabit parallel social environments. With only six months between Nosipho's and her mother-in-law's breast cancer diagnoses, their divergent yet intrinsically connected worlds were brought into direct conflict, as the younger woman sought to assert her gender independence and deal with her pressing biomedical needs while the older woman sought her African social cultural roots to deal with the multiple

physical and psychological traumas wrought by breast cancer. Great strife ensued between the two women at a time when their shared cancer experience should have served as a delicate tie that binds.

Pink-ribbon awareness campaigns and literature that do not include the African women's lived experiences of coping with breast cancer amidst poverty and other psychosocial stressors make it harder for them to cope with their physical and psychological trauma. This is because their fears, grief and multiple losses are not acknowledged in the prevailing breast cancer dialogue. It is perturbing that age, class and racial biases continue to persist and affect young women like Nosipho. Indigent African women cannot relate to the standard United States and European style breast cancer testimonials of courage over adversity because the witnesses depicted in the literature inhabit a very different social environment: they are almost exclusively white, over 55 years old, affluent homemakers and well educated.

Informal discussions with women in the townships unearthed and highlighted unique testimonies of sociocultural, socioeconomic and religious challenges that impede their seeking of early treatment for cancer. We saw the intricate challenges that Nosipho faced in negotiating her dual milieus encompassing African sociocultural marital status and her liberated, young professional status. She understood her rights over her body autonomy but had to endure mental anguish to exercise them. Professional psychotherapy counselling would have been of benefit to her and her partner, but financial constraints and lack of mental health services in the South African public sector denied them that option. Similar lack of access to comprehensive oncology services confronts women and men living with cancer throughout the African continent.

4. Conclusion

Research advocates have a critical role to play in dialogue cancer control and care in Africa. They bring a wealth of their lived disease experience together with a unique grassroots understanding of local communities. Of significance are the narratives of patients, which are often withheld from traditional research academics. The framework and experiences shared in this chapter provide guidelines for research advocacy in Africa. An ideal framework should comprise five important features: (a) partnerships between advocates and researchers, (b) public and private support and investment, (c) a research system that values patient input and embeds research advocacy, (d) a regular flow of individual citizens willing and able to be research advocates, and (e) ongoing training and preparation for advocates. However, the success of research advocacy lies in the structure of and the commitment to meaningful engagement.

Advocates can and will make a difference in cancer awareness, prevention, incidence, care and outcomes across Africa. The only requirement is action, moving away from the rhetoric that calls for urgency and the habitual making of recommendations and grand statements to practical steps, assignment of action, reasoned collaborations and implementation of good practices. The call to action in Africa is to have cancer research advocates (a) represented on research teams developing grant and research protocols, (b) as reviewers on cancer grant review panels, (c) actively involved in research protocol reviews by institutional review boards; (d) supporting efforts to recruit and retain research participants, (e) interpreting study results for the public, and (f) actively disseminating cancer research results for effective cancer control and prevention. These all are feasible, all doable and all necessary.

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Chapter 12

Research dissemination

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Chapter outline

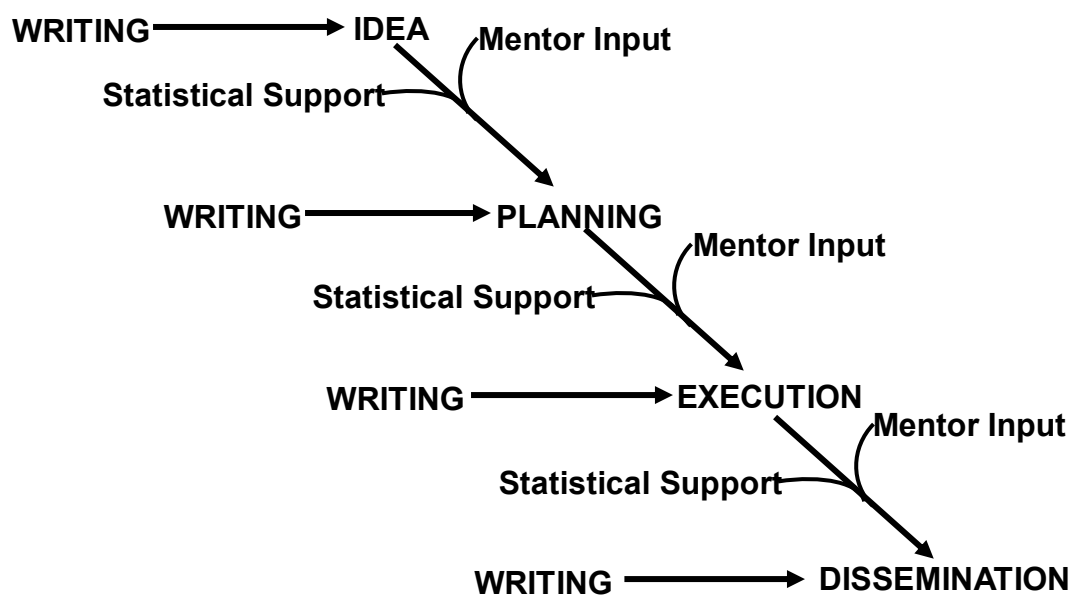
1. General principles of research dissemination
2. Questions the researcher should ask
3. Maximizing publication success
4. Manuscript writing
5. Authorship
6. Ethics in research dissemination
7. Conflict of interest
8. The editorial process
9. Summary

1. General principles of research dissemination

Research dissemination is an integral part of the research process. Dissemination involves the communication of research results to other scientists, the community affected by the research, policy-makers and others who are likely to benefit from the knowledge generated in the research.

As shown in Figure 1, the process of research dissemination is not limited to the final stages of the research process but is a continuum of activities that culminates in an oral presentation or preparation of an abstract, a poster presentation, a manuscript or some other output. The process covers all the stages of research from the conception of a research idea, going through study planning and execution and report writing, to final formal dissemination of the research results. Figure 1 identifies the critical inputs for each stage along the research continuum. The first such input is statistical support, including epidemiological study design, power and sample size considerations, and statistical analysis considerations. Input from statistical and epidemiological colleagues should be incorporated early and revisited regularly in the research process in order to have a research product that can be effectively disseminated, for example in the form of high-quality research publications. Advice from mentors is a critical input, particularly for junior researchers. Such mentors may include academic advisers who provide guidance on the best research course to maximize career opportunities and scientific experts who comment on and participate in the research. Many researchers may consider the writing of a manuscript as something that occurs in the final phases of the research process. However, to optimize the quality of the final research product, writing should occur at every phase of the research continuum. The background information written during the formation of the research ideas can be used in the manuscript's introduction and discussion sections. Material prepared during the "planning" phase of the research continuum may be used in the manuscript's materials and methods section, while what was written during the "execution" phases of the research can be used in the manuscript's results section. While it is likely that the manuscript will require substantial discussion, editing and revision through the research process, writing as the research progresses instead of waiting until the research is completed can benefit the process of the research and improve the final product.

Figure 1: Research dissemination continuum



2. Questions the researcher should ask

Early in the research continuum, the researcher should ask a number of questions in order to ensure optimum dissemination outcomes for the research. These include:

What findings might be important?

While it is not possible to know the outcome of the research, the hypotheses that are laid out early in the research may guide the dissemination process. Knowing the potential outcomes of hypothesis testing will provide direction for the types of meetings, journals or other venues for research dissemination.

Who is the audience?

Often the research community is the audience of the research dissemination. However, the researcher can also consider other audiences who may benefit from knowing about the research results. Clinically relevant research may be of interest to clinicians who may change their clinical practice if the research is ready for translation. Policy-makers are often interested in research if it helps to guide utilization of resources such as health-care expenditures or planning. Policy-makers may also be interested in the health economic implications of the research. The audience will differ from field to field, but consideration of the audience who may be interested in learning about the research may help to focus the types of dissemination avenues that the researcher considers, and these may include non-traditional media.

How will the research be disseminated?

In addition to being published as full research articles, the research results may be appropriate for dissemination through other venues. These include short reports, for example for important but more narrowly defined results; letters to the editor, for example to discuss related issues raised previously in a journal or to bring up relevant aspects of the research that are not amenable to publishing as a full article; editorials, for example to provide commentary on research; and oral or poster presentations, for example to present the research to an audience of interested parties and obtain feedback about the research methods

and results. Consider the suitability of these as options when trying to communicate the results of research to relevant communities.

3. Maximizing publication success

Features of successful research papers

Papers that are most likely to be accepted for publication share some common features. They are based on well-justified and clearly stated hypotheses and address well-defined, specific aims. The methods that are used are adequate to address these aims. They use precisely defined and well-calibrated measures and end-points, and employ strong statistical methods. While this will vary substantially by topic and field, the better papers will contain enough information to tell a story, that is they address a solid set of aims. The researcher should avoid the temptation of splitting up parts of a research study into too many small and less complete papers in order to have a large number of publications. Researchers should acquaint themselves with both good and bad articles in their field to understand the range of research that is being published.

Choosing the right journal

Focusing the goal of research dissemination is another critical factor in the success of the researcher and getting the research results to the appropriate consumer. The research should focus the dissemination goal by identifying the appropriate journals in the field. With the help of mentors and other colleagues, one can become familiar with the journals that publish work in your area. In some cases these journals will be sponsored by professional societies to which the researcher or peers in the field belong.

As the researcher becomes familiar with the literature in the field, he or she should note the journals cited and which will publish related work more often than others. The researcher should look at the papers they cite in his or her own work field. These citations often identify journals that may be interested in the researcher's work. Reading the "information for authors" available for each journal is also a good way of understanding their scope.

To ensure wide dissemination of the research, in this century widely circulated paper journals that are not as important as journals indexed by PubMed or other online databases, although most high-quality journals will fall into both categories. Papers in journals available online or via "open access" (i.e., without charge to the reader), and those that can be easily found via online database searches will reach the target audience.

The researcher should consider submitting work to the "best" journal, that is, the journal with the highest impact possible. While some research papers will not be appropriate for very high-impact journals, the researcher should consider such journals for the very best work. Many of these journals accept only a small proportion of submissions, but it is important to attempt to publish research in them to get the maximum exposure for the research and maximum positive impact for the author's career.

4. Manuscript writing

Writing a manuscript that summarizes research results is one of the most important activities in academia. Careful consideration of the approach to writing and dedicating sufficient time for that work is critical for academic success.

A common roadblock for researchers trying to complete a research project is the inability to set aside time for writing. Research dissemination, including writing abstracts or papers and preparing presentations, involves a substantial amount of effort. Time taken up by delays due to revision requirements or rejections of the manuscript or its presentation should be built into the time frame of the research dissemination process.

How does a researcher, particularly a busy one, find time to complete the research to the point of a published paper? Figure 2 suggests a framework to help the researcher to determine how to set aside time for the dissemination of research. Figure 2 presents a 2 x 2 contingency table with two axes that define tasks as “important” or “urgent”. Tasks that are both important and urgent (cell A) such as patient care and family responsibilities must be dealt with and should not be easily put off. Tasks that are urgent but not important (cell B) may also be unavoidable, but if time spent on them can be limited, more time will be available for other, higher priority academic needs.

Figure 2: Prioritization of research activities

| | | | |
|----------------|-----|-------------------|----|
| | | <i>Important?</i> | |
| | | Yes | No |
| <i>Urgent?</i> | Yes | A | B |
| | No | C | D |

5. Authorship

Discussion of authorship should occur early in the research process. Agreement about who the eligible authors will be and the contribution they will need to make to be a named as authors can avoid misunderstanding and confusion about the role of each individual in the research process. Authorship is generally given to those who provide significant intellectual input and contribute to the development of the manuscript. These contributions can include technical input, such as development of methods or acquisition of data, and scientific input including conception and design of the study and analysis and interpretation of the data. Contributing to the writing and approval of the manuscript should be a criterion met by all authors. A good rule of thumb is that each author should be able to take public responsibility for their appropriate portions of the paper content and to explain the overall message of the research. Each research team should define who will be listed as an author or who is going to be listed in the acknowledgements. Many journals have criteria for determining authorship, and these guidelines should be adhered to closely.

6. Ethics in research dissemination

Ethical practice in research dissemination is important not only to maintain the integrity of the literature but also to ensure the researcher’s career and reputation are protected. It is critical to publish a result only once; duplicate publication of the same research is not appropriate. If the research reported in one paper is relevant for another paper, it should be cited not repeated in the new paper.

Honest errors can occur in research. These can be corrected via errata or retractions of published research. Minor errors including typographical errors or misstatements may be eligible for errata. The researcher is obligated to contact the editor of the journal in which the research was published to report such errors. More serious errors that compromise the entire message of the paper may require a retraction of the research. It is incumbent on the researcher to report these issues when they are found. Many journals now have

sophisticated software to identify previously published material usually at the time of submission, and have means to detect plagiarism and other scientific misconduct. It is never in the author's interest to provide incorrect, plagiarized or fraudulent data.

7. Conflict of interest

Conflict of interest may arise if an author has financial or other relationships that may influence the presentation of the research or cause the author's judgment to be called into question. For example, research published by authors who may gain financially from the results would be considered a conflict of interest. Conflict of interest may also be associated with personal relationships such as family ties or sources of project support. Conflicts of interest will not deter the researcher from publishing their work, but all potential conflicts must be disclosed at the time of manuscript submission. Most journals will require statements on conflict of interest by all authors.

8. The editorial process

Each research discipline and journal will have slightly unique editorial standards and practices, but there are some general principles that cut across most publications in the field of cancer. Typically, after the manuscript is submitted (often online) it is referred to an editor for review. The editor will consider whether the manuscript is within the scope of the journal, whether it has sufficient impact to be of interest for the journal to publish and whether it is likely to be acceptable for publication because it does not have any obvious or serious flaws. In some cases the decision to "reject without review" is made if the manuscript does not meet the initial criteria of the editor. This decision may be distressing to the author, but, in fact, a quick decision is helpful to authors since it does not delay the submission of the manuscript to another journal. In many cases, the "reject without review" decision does not mean the manuscript is of poor quality; it might just be that the manuscript is not within the scope of the journal.

If the editor finds the manuscript to a sufficient match with the journal, the manuscript will be assigned one or more peer reviewers. These individuals are experts in the field and have qualifications to review the methods, results and conclusions found in the manuscript. In some cases, a third reviewer is requested if two reviewers cannot agree on the decision, and a statistical reviewer may be needed for the data analysis.

Once the peer review has been completed a decision will be made. The categories of these decisions vary by journal, but broadly the messages are the same:

- **Accept as is:** The manuscript is acceptable for publication without revisions. This decision is generally uncommon.
- **Accept with minor revisions:** The manuscript can be accepted, but a few minor changes are required before publication. This decision is also relatively rare.
- **Major revisions required:** The manuscript has strengths, but there are important concerns that must be addressed by the authors before the manuscript is acceptable for publication. The authors are usually asked to revise and resubmit the manuscript with a detailed description of the changes that were made in response to the reviews. The authors should respectfully and seriously address all points in the review even if they disagree with the reviewer's statements. There is usually no guarantee that the revised manuscript will be accepted. The revised manuscript may be sent back to the original reviewers or to new reviewers; this is at the discretion of the editor. The editor may also make a decision based on the reviews without getting further input from the reviewers.
- **Reject:** Rejection usually results from the combined decision of the reviewers and the editor. Rejections are very common for high-impact journals.

The decisions are usually made based on a combination of the critiques by the peer reviewers and the general impression about the novelty or significance of the research. A manuscript may be rejected even though the study design, methods and analysis are appropriate, because the impact of the work is judged to be low.

The reviews, even in the case of a rejection decision, are of great value to authors. The review provided important information about how to improve the manuscript that may be of value to the researcher's ongoing research or other submissions to that journal or a different journal.

How does an author deal with rejection of a manuscript? First, every author, even the most well-known and respected scientist, has had a manuscript rejected. If the manuscript is rejected without review, it should be reformatted and submitted to another journal. If it is rejected after review, use the information obtained in the reviews to improve the manuscript. If there is evidence that the rejection should be contested because it was based on inappropriate reviews, including bias or possible unethical behaviour, the editor should be notified of the concern. Such rebuttals to a rejection should be fact-based and approached with due respect to the editor. Harsh or unprofessional statements and threats are not helpful in making the author's rebuttal.

9. Summary

Research dissemination is a key part of the research process. The research does not have value to the academic, clinical, public health or policy communities if it is not appropriately communicated to the right audience. Early and repeated consideration of the various avenues for dissemination is needed to maximize the value of the research.

Appendix

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