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In this issue:

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From the Editor in Chief

The theme for this issue is the 'ethics of clinical trials and post trial benefits'. The number of clinical trials in developing countries has surged in recent years; however the legal and ethical frameworks are not always in place. There has been a substantial debate on the ethical concerns of research done in developing countries. In general controversies have centered on 3 issues: the standard of care, reasonable availability of interventions during and after trials and the quality of the informed consent. Developing countries often provide lower costs of conducting research and the availability of large populations of "treatment-naive" patients, not previously exposed to drugs or sometimes research or clinical trials. An incentive for developing countries for the participating in research, in addition to the academic achievement for scientists is in the promise of advancing medical science and access to the latest medications in addition to service provision during the conduct of the study.

Although the process of putting in place both legal and ethical frameworks to protect participants has rarely advanced at the same pace as medical science, much progress has been made to protect research subjects since the development of the Nuremburg

code which was develop in in response to the medical research conducted during the second World War.

Prior to the 1947 Nuremberg Code there was no generally accepted code of conduct governing the ethical aspects of human research. The Declaration of Helsinki developed the ten principles first stated in the Nuremberg Code which specifically addressed clinical research, reflecting changes in medical practice from the term 'Human Experimentation' used in the Nuremberg Code. A notable change from the Nuremberg Code was a relaxation of the conditions of consent, which was 'absolutely essential' under Nuremberg. Now doctors were asked to obtain consent 'if at all possible' and research was allowed without consent where a proxy consent, such as a legal guardian, was available.

The declaration has since been regarded as the most widely recognized source

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A Word From the Director

Welcome to this issue. This issue's theme seeks to address the concerns of the increasingly global nature of health research, and in particular the conduct of clinical trials involving human participants in the developing world. The main ethical challenge arises when such research is conducted in a background already facing many public health challenges, as is common in developing countries. Some of the challenges include affordability, availability and accessibility of drugs for treatment, and, generally, provision of adequate medical care. Indeed, the medical care that may be extended as a benefit in a clinical trial conducted in such an environment may be the only available medical care. Furthermore, a participant suffering or who has had a past episode of the disease under study, will view the study as an "opportunity" to cure a health problem without any financial implications on his/her part, and hence participation may be regarded as due to inducement rather than free consent.

Another important aspect to consider in clinical trials is that the benefits of research must also accrue to the group from which the research participants are selected. With the new Kenyan constitution, the administration of provision of health services will be decentralized; KEMRI understands and upholds the principle of ensuring that populations, especially vulnerable ones, should reap the potential benefits of the research involving that group, and by extension, mankind. KEMRI has the national mandate of providing technical assistance to strengthen the use of research in formulating effective new health policies for better healthcare and to protect research participants as the country devolves and as health care services are managed at the county level. KEMRI will seek to develop relevant county specific health research agendas tailor made to address the specific health needs for each county. KEMRI's presence in every county is thus important during and beyond the transition. With regard to capacity building for health research, KEMRI is well placed to help health institutions develop capacities to monitor and evaluate their overall effectiveness in health care delivery and prevention of ill health. As Kenya devolves andseeks better health for all, KEMRI will play a critical role in delivery of human health research, at both the national and county levels.

Dr. Solomon Mpoke, Director KEMRI

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of medical guidance for biomedical research. Since its adoption in 1964, the Declaration has been revised five times. The most recent revision, however, has resulted in considerable controversy, particularly in the area of the ethical requirements surrounding placebo-controlled trials and the question of responsibilities to research participants at the end of a study as stated in Paragraph 32. This section 32 is currently being reviewed by the World Medical Association Group. http://www.wma.net/en/50events/20otherevents/50doh2013_1/index.html

In this issue our focus is on research sites where KEMRI has conducted large clinical trials. Two articles focusing on some of the ethical dilemmas and logistical challenges experienced while conducting clinical trials and how researchers in Kisumu HIV studies and Malaria genetic studies in Kilifi have made efforts to deal with this. We also feature an article on the collaborative partnership between the KEMRI Wellcome-Trust researchers and the communities they are engaged with. We have also included an interview with the new chair of the KEMRI Board of Management, an eminent researcher and her vision for KEMRI moving forward.

The challenge that we will continue to face as a research institute, is balancing the needs of biomedical research whilst upholding protection of research participants and communities. We hope that this will go beyond robust review of research protocols. As the premier health research Institute in Kenya we want to set standards. We want to go beyond approval and annual renewals and undertake education of researchers and monitor approved protocols to improve the quality of the research undertaken. I wish you enjoyable reading and hope that you find this issue informative.

Meet the New Chairperson of the KEMRI Board of Management

An interview with the new KEMRI Board of Management chairperson, Prof. Ruth Nduati MBChB (UoN) M.Med (Paed) (UoN); MPH (Epidemiology and International Medicine) (UW)

Tell us about yourself

I am a pediatrician, and an epidemiologist. For the past 20 years I have been teaching at the University of Nairobi in the Department of Pediatrics and Child Health. I am also involved in research focusing on Prevention of Mother to child Transmission of HIV and have conducted research in clinical trials and programme implementation in this area.

As the new chairperson of the Board of Management, what are your short- and long-term goals to drive forward KEMRI's scientific agenda?

It is a real honor to have been appointed as a chair of the KEMRI board. I have been on the board as a member but this appointment is a new opportunity and a challenge that I am thankful for. It is a very unique opportunity indeed. My first thought is that we need to increase the research productivity in KEMRI, and we need to feel good about doing research.

I would like KEMRI to be a place where people feel good when in the field, dashing to work, getting involved and asking all the many questions that we need to ask so that we can actually contribute to improve the healthcare for Kenyans. I would like to see an environment of excitement about research and clear research output such as won grants, increase in number of proposals from institute staff and the policies and guidelines that are being implemented in our healthcare system. We have a collection of people in KEMRI who are really smart. It is a very unique population, the best that Kenya has, and among the best in Africa. I hope that by being here I can help to contribute by creating an environment where KEMRI can be able to achieve those goals, of course I can't do that as an individual, and we all need to play our roles. As a team we can move forward.

We are looking forward to working with the new devolved government particularly the county health management teams. The KEMRI board of management is determined to enjoy the opportunities that county governance is going to offer Kenyans. We are an institution that is strategically of national and international importance.

KEMRI plays role as a leader in biomedical research in responding to the challenges and emergencies that occur, the universities of course also contribute to biomedical research, but KEMRI is unique in that we are the ones who respond to health emergencies and anchor information that help in health policy development in Kenya. We need to start engaging with county government, as the Ministry of Health continues to devolve healthcare delivery services to county level. We should get involved especially in health systems research and translating our research findings into a language that is easily comprehensible.

We also play an important role in capacity building. With the University Act which offers an opportunity for research institutes of strategic importance to become degree awarding institutes, I think we should grow the ITROMID programme offered within the KEMRI Graduate School of Health Sciences to a fully-fledged university offering high level training in biomedical research.

How do you plan to stimulate more in house research especially from female scientists?

I don't think we are in danger of having too few women scientists in research. In fact, among the generation coming on board may have more women scientists than men. What we need to do in KEMRI is to have a system of training scientists on how to do research, especially in epidemiology and biostatistics which are core courses for someone to be a researcher. The grants awarded to staff from KEMRI resources, creates a sense of pride. Scientists need to be encouraged to apply for more grants. Winning a grant I think is highly motivational. The increased number of grants coming to the institute is very important in increasing and measuring productivity in addition to performance based contracting, pioneered globally by Kenyan government.

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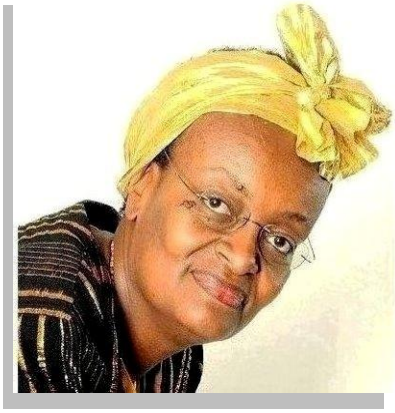
Additionally, should the KEMRI Graduate School get a charter more scientists will be involved in teaching and this, in itself will stimulate creativity. A chartered graduate school will increase the research productivity of the institute and this is how many other institutions have succeeded.Those are basically the three ways we can be able to increase the output.

You are renowned for your work in breast feeding and transmission of HIV study, as a researcher what ethical challenges did you face during the study?

The first challenge for us was writing the proposal. In 1985 The Center for Disease Control and Prevention (CDC) gave the guideline that HIV infected women should not breastfeed after studies showed transmission of the virus through breast feeding. Then in 1987 and 1992, WHO said there was little transmission of HIV through breast feeding and advised HIV infected women in resource limited setting especially Africa to breast feed. So the question was why is a mother in Africa different from a mother in Europe? It was a clear situation of equipoise and we did not know what was better, to breast feed or formula feed. That's how we ended up doing a randomized trial on breast feeding verses formula feeding.



Prof. Ruth Nduati

During the study we held several discussions on the ethics of doing such a study. We even wrote a paper which did not get published, on ethical issues to consider in such kind of research such as; the informed consent, the principle of doing no harm and social justice. Other ethical issues included status disclosure to the pregnant women partners after offering HIV tests.

We also did some formative work and found out that the men felt they should know their wives' status first and then they would decide whether to disclose to them. This, of course this is contrary to the practice of medicine as it violates the patient-doctor confidentiality So we had to figure out how to deal with that and we encouraged the partners to come and get tested too. However, the challenge was how to face the couple so that we would not create an impression that the wife had known she is HIV infected and had not told the husband. Dealing with those sorts of counseling scenarios presented a lot of challenges. We however, applied the principle of do no harm to individual and also do no harm to family. So when faced with such a scenario, we asked if they had informed their partner? If yes we picked it up from there, if not we asked if she would like us inform him, then in that case we would do a counseling right from scratch and inform the men that his wife had been tested, and was HIV infected, and we would encourage them to get tested too.

Post clinical trials benefits is a critical issue that needs to be addressed especially given the fact that most studies are conducted in developing countries. As the head of the premier institute what mechanisms will you put in place to ensure that participants access post clinical trial benefits?

First of all the strengthening of the ethics research committees is one of the strategies that we have clearly identified that can contribute to ensuring that participants have access to post trial benefits.. Secondly, creating awareness on ethical issues through training, such as the online Collaborative Institutional Training Initiative (CITI) which is a subscription service providing research ethics education to all members of the research community.

In the PMTCT studies that I have been involved in, there was direct benefit to the mothers. We provided good quality healthcare to the first cohort throughout the study, although they did not benefit from ARVS at that time. Through these studies we were able to evaluate feasibility of integration PMTC and maternal health care (MCH) although we had already been doing it as part of good recruitment practice during the trials. We were working in many centers in Nairobi offering testing as part of the Anti-natal care (ANC) screening package.

In 1999-2000 we began implementation programmes on integrated PMTCT and MCH services, before the Presidential Emergency Plan for AIDS Relief (PEPFAR) was initiated in 2004. Funding from PEPFAR enabled us to recruited women who had participated in our study to be counselors especially those who were desperately poor and this provided them with some form of income and improved their self-esteem. However,

we need to note that the benefits of clinical trials do not come immediately. It may take 10-20 years, especially for molecular biology research studies like the ones we are currently doing. Therefore what we must do is make sure follow-up done on research participants should be translated into a skill in healthcare system and must be intensified especially for chronic disease management, doing monitoring appropriately and getting back to clients with results on time.

An institute wide survey on the current regulatory system was conducted and one of the challenges identified was the lengthy time of review, what suggestions do you have in improving this process?

The current system of review was developed when the institute was small. From my observation after coming into KEMRI is that we have too many layers, for example the scientific and ethical review functions should be made one stop, and I think it is an artificial division, because a poorly designed study is unethical. Ethics is not all about informed consent.

Over time the Institute has grown and this necessitated the need to have different divisions of the ERC so that we have a much faster review process than we do now. Adopting an electronic system is good in terms of tracking, we must have a quick turnaround time in proposal review to grab some of the opportunities that come and have got a very narrow window, we may need to ask ourselves if you are putting a proposals in response to call for grants where they are timelines, should a researcher submit first before seeking ERC approval to avoid loss of opportunities.

What do you think about KEMRI getting external proposal reviewers, and where can KEMRI get these reviewers?

I support the idea. KEMRI can get reviewers from local universities. This will be an opportunity for KEMRI ERC to build capacity in proposal review by bringing people on board and training them on how to review proposals and generally this increases awareness on research ethics.

On a lighter note what do you do on your free time?

All sorts of things, I like to spend time with my family, I also enjoy playing piano sometimes, I like knitting and I enjoy reading and writing a lot.

Parting shot

This is the beginning of the rest of our lives, so what is in the past can't be changed we need to offload it. Each one of us has 365 days in year, 24hrs in a day how one utilizes that time will determines if one will move forward. Change begins with each one of us. If we continue working together as a team we can be extremely successful. I think this devolved government gives us a real chance for success because KEMRI does research in most parts of the country. . It is a fantastic opportunity as we go forward.

Call for Articles for the newsletter:

The KEMRI Bioethics Review is eager to relay information about ethics activities that occur at KEMRI and elsewhere, on a regular basis, and encourages newsletter submissions from all members of the Institute staff. The theme for our next issue is Public Health Research and Ethics. Please submit your articles by 22nd of May 2013. Please note that the editorial staff reserves the right to edit submitted items.

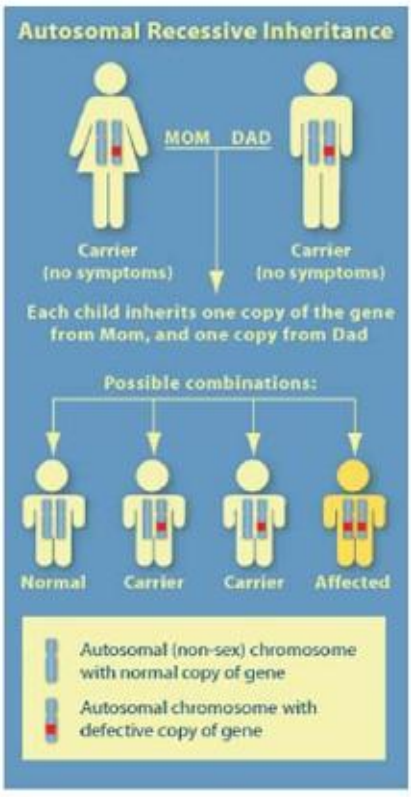
Researchers' responsibilities for disclosing genetic findings during studies

The Challenge Presented by Sickle Cell Disease in Malaria-endemic Areas in Kenya

By Vicki Marsh, Francis Kombe, Dorcas Kamuya and Sassy Molyneux (Health Systems Research and Community Liaison Groups)

Researchers' responsibilities to share genetic findings identified during the course of studies have been strongly debated in the literature, drawing on a range of ethical principles in which respect for autonomy, maximising benefits to participants and prioritization of resources tend to predominate. In this article, we aim to highlight a local aspect of this debate for many types of research conducted in malaria-endemic parts of Kenya that include screening for Sickle Cell (SC) Disease, the most common serious single gene disorder worldwide. Three quarters of an estimated 300,000 to 500,000 children born with SC disease worldwide every year are born in Africa [1], a situation explained by the evolutionary relationship between the SC gene and inherited resistance to malaria.

SC disease, an autosomal recessive condition, is an inherited abnormality of red blood cells. Affected children inherit two copies of an abnormal haemoglobin gene, one from each parent. For individuals with one copy of the abnormal gene, described as having SC trait or being a carrier for SC disease, there is a 1 in 4 chance of future children being affected by the disease where both parents are carriers. From a biomedical perspective, a high potential for benefit from sharing research-generated SC disease findings stems from a positive health impact of comprehensive forms of health care. Without care, symptoms can be very severe and life threatening [2]. Although environmental and genetic factors influence severity, without care many children in malaria endemic settings are likely to die in their first few years of life [3]. In contrast, quality of life is significantly improved where comprehensive care programmes are in place [4], leading to a median adult survival of 48 years [5]. SC trait is generally seen as a benign condition [6] whose main implication is an increased future reproductive risk for the disease [7].



Given the relationship between the SC gene and innate malaria susceptibility, screening for SC status is a relatively common component of many different types of health research in malaria endemic settings, where SC status may be the focus of the study or act as a risk factor or confounder for a different primary research question. For example, at KEMRI CGMR-C in Kilifi, where around 1% children under one year of age have SC disease and 18% carry SC trait, screening for SC status has been included in research on malaria, pneumonia, Human Immunodeficiency Virus/ Acquired Immunodeficiency Syndrome (HIV/ AIDS) and malnutrition in young children as well as in studies on the prevalence and clinical manifestations of SC disease. In all these situations, the question of researchers' responsibilities for sharing this information is raised: Should researchers always try to share information on SC status, including on SC disease and SC carrier status? If so, why, and how should this be done? And what does this imply for the way research is conducted?

In the general debate on the importance of sharing study-generated genetic information

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with participants, assuming tests are reliable and accurate, a key issue is the practical significance of the genetic information to participants. In addition to this 'clinical utility' of genetic information, other social forms of benefit are important, including knowing about future reproductive risks [8]. Many argue for a right to know about personal genetic information even in the absence of a 'practical' importance. A widely accepted principle is that participants' own views should in any case inform any understanding of the nature and importance of potential benefits [9] since researchers may not be in a position to judge what is useful to others. For SC trait, in addition to generating participants' awareness of future reproductive risks, alerting the wider family to this risk and respecting their rights to ownership of genetic information are seen as important reasons for disclosure[10].

On the basis of these ethical arguments, the responsibility for researchers to share information on SC disease when this is discovered during the course of studies -particularly where this is likely to be otherwise unknown to participants at that time - seems very high. At KEMRI CGMR,C, this situation generally occurs during research involving young children, either because screening at this age is presumptive (that is, in the age group of about 6 months to one year, before symptoms appear in affected children) or because the biomedical nature of the condition has not been recognised by parents. The latter situation, from the few reports available in malaria-endemic parts of Africa, is likely to be common [11-13]. Given the fleeting, severe and variable symptoms of SC disease in young children, including severe pain and crying, it is difficult for parents to recognise this syndrome as one disorder, let alone as a specific inherited condition. In addition, our research suggests that health workers may not consider this diagnosis until children have repeatedly been brought to clinics. In this life-long condition, traditional healers are commonly consulted, and parents may in any case commonly move backwards and forwards between different types of health providers – biomedical, faith-based and traditional – in their desperation to find help. The potential for carefully communicated information and provision of health services to limit the severe harms associated with low understanding of this condition makes the ethical basis of arguments for disclosure very strong.

In practice, arguments against disclosing SC disease findings in research are considered most compelling where clinical and other services are not available or insufficient [14]. In these circumstances, and in spite of potential charges of over-paternalism, or even complacency, it is difficult for researchers to disclose SC disease findings unless they can mobilize these services themselves. At the same time, research involving SC disease screening may be critically important in the population, for example, to establish the prevalence of the disorder to plan for services; or in malaria vaccine trials in areas where the mortality and morbidity of this infectious disease are high. But where clinical services are not available, or not accessible for reasons of geography or economic cost, there are particular challenges for researchers in assessing whether the use of research resources to supplement government clinical services would be justified [8]. The life-long nature of this condition makes this a particularly difficult situation. Other arguments against disclosing SC findings during research include the risk of the study being seen by participants and the wider community as a form of health check, that is, acting as a form of a 'diagnostic misconception' and undermining understanding of the research itself. For SC trait, there are also potential risks that the information on carrier status will not be well understood, leading to unnecessary fears, stigmatisation and - for children screened - of undermining their autonomy [15].

At KEMRI CGMR-C a close collaboration has been built up over time between researchers and government health providers at Kilifi District Hospital to ensure a platform of clinical services is consistently available to support different studies conducted at the centre, including services to study participants and non-participants. These include the provision of a dedicated weekly clinic for children affected by SC disease. Given this availability of care, researchers in Kilifi generally disclose study-generated findings on SC disease to affected families, but currently not on SC trait. Community liaison activities across the programme constantly aim to build understanding of research and counter therapeutic and diagnostic 'misconceptions' of research. However, a challenge remains for researchers concerning the scope and sustainability of support needed for a lifelong condition where skilled counselling is an

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important part of limiting harms, given the distress, anxieties and risks of blame within families, which are often highly gendered [11].

Given the public health nature of this chronic condition and the potential for prevention or reduction of impact, including through premarital or newborn carrier screening programmes, the role of government health authorities in developing and implementing public policy for SC disease seems clear. Like HIV/AIDS, if these services were widely available, research involving screening for SC disease could be done with far fewer concerns about the ethics of screening and disclosure. But currently SC disease has a low profile in Kenya, related to the past - now changing - emphasis on communicable disease control. Illustratively, SC disease is not currently included in national disease surveillance activities.

While an absence of effective public services can be argued to limit researchers' responsibilities for disclosure, our research on SC diseases shows the moral challenges that failing to disclose information on this condition implies. For this reason, it seems to us that the ethical importance of limiting harm in this situation, together with the public health nature of SC disease, strongly underline the importance of researchers working in prior partnerships with government health authorities to ensure that - as far as possible - disclosure and services support the long term interests of study participants. In other words, although researchers may not have responsibility for disclosing SC disease findings during studies where clinical services are not available, researchers do have a responsibility to build supportive partnerships with government health authorities to provide these services within current policy guidelines, including training of health providers where indicated. Further, we argue that they have a strong responsibility to work within these partnerships to inform future policies to strengthen the ethical basis of their research.

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Ethical, Moral, and Logistical Challenges in Conducting Clinical Trials

By Maria J. Oziemkowska, Research Co-ordinator , KEMRI/CDC Programme, Kisumu

A clinical trial can be defined as a prospective biomedical or behavioral research study of human subjects that is carefully designed to answer specific questions about the safety, efficacy and effectiveness of biomedical or behavioral interventions (drugs, vaccines, treatments, devices, or new ways of using known drugs, treatments, or devices). If a clinical trial is for a vaccine, the study could also be designed to test the immunogenicity of the test vaccine or how well the vaccine is able to stimulate protective immune responses. Clinical trials are a central tool for the creation of medical knowledge and its implementation. They are the gold standard by which the obtained knowledge is evaluated.

The term 'clinical trial' comes from: Trial, which is of Anglo-French origin from trier, meaning to choose, sort, select or try and Clinical, which is of French (cliniquè) and Greek (klinikè) origin; klinikè pertains to the practice of medicine. The feminine form of klinicos, from klinè, means couch or bed for the sick. Today, the use of clinical trial in medical research covers a wide variety of designs ranging from uncontrolled observations involving the first use of treatment in humans to a formal experiment, complete with a control treatment and randomization (Clinical Trials: Design, Conduct, and Analysis, by Curtis L. Meinert, 2012).

The conduct of clinical trials is complex and the complexity increases for trials done across multiple, international settings and for those sponsored and conducted by multiple partners and involving diverse funding mechanisms. As the scope and pace of clinical trials increases worldwide, the demand for trial sites in both developed and developing countries increases and so does the challenges that are associated with the conduct of clinical trials. These challenges are numerous and could involve the design of the study, getting ethical and regulatory approvals, recruitment and training of qualified and experienced personnel to run the study, ethical issues in mobilization and selection of study participants, compliance with the requirements of good clinical practice (GCP), and community perceptions and expectations. In addition, management of a phenomenal amount of paperwork or documentation, budgetary issues, and maintenance of relationships with a variety of trial personnel, including principal investigators (PIs), medical and clinical staff, regulatory monitors, sponsors, laboratories, insurance companies contribute to other challenges.

This article will focus only on some of the ethical and logistical challenges experienced while conducting clinical trials. The challenges described here are based on personal experiences while working in clinical trials in the United States of America and in Kenya for more than twenty years. The described challenges are mostly accounts from only one perspective and they may not capture fully the complexity of clinical trials and their ethical issues. It is hoped that the article may open a debate in this Newsletter on the topics highlighted.

There is a long history of disregard for individual rights of subjects in clinical trials. As a result of gross abuses, in 1964, the World Medical Association (WMA) developed the Declaration of Helsinki that laid down the guidelines of ethical principles to be followed when conducting medical research that involves human subjects, including research on identifiable human material and data. These main principles are: beneficence, non-maleficence, autonomy and justice. Although the Declaration is addressed primarily to physicians, these principles should be followed in all research involving human subjects.

To protect the rights, safety, and well-being of trial subjects consistent with the principles of the Declaration of Helsinki and to assure that clinical trial data are credible, in 1996 the International Conference on Harmonization developed Good Clinical Practice (GCP) guidelines. GCP is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects. The main elements of GCP are: scientific validity, fair subject selection, favorable risk-benefit ratio, independent review, informed consent, and respect for trial subjects,

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including confidentiality. All these regulations have immensely contributed to the fact that the clinical trials are conducted far more ethically and safer now than they were some decades ago. The significant reduction of gross violation of ethical practices and increase in global organizations that play a watchdog role in monitoring adherence to GCP in clinical trials has allowed researchers to focus more on subtle ethical and logistical challenges encountered in the day-to-day trial activities such as the ones highlighted below.

Informed consent

The issue of informed consent remains problematic not only for trials involving vulnerable population such as children, incompetent adults, emergency situations and the critically ill. The scientific complexity of clinical trials leads to complexity of informed consent process. Standard discussions during the development and approval of consent documents do not always reflect the complexity of negotiations that the consenter will be involved in during the consenting process. The demands of regulatory bodies, sponsors, and the institutional review boards (IRB) or ethical committees to include certain standard wording in the informed consent form sometimes undermines the ability to more appropriately shape the drafting of the consent form.

No matter how well the Informed Consent Form (ICF) is designed and written, it is still a challenge to absorb it fully by some participants, especially from rural settings or illiterate participants or parents/legally accepted representatives (LARs) of children participating in clinical trials. It is challenging for the clinical trial team to explain some of the science and/or procedures involved. The preparation of patient information, including consent forms, in different languages (e.g. Dholuo and Kiswahili in Kisumu) adds another challenge to the consent design and consenting process. Some of the English terms have no direct equivalent in, for example Dholuo, and it becomes challenging for the consenter to convey the information to the potential participant in the manner that exactly mirrors the English meaning of the word. It is difficult to translate to the local language terms such as randomization, placebo, adjuvant, immune response, blinded, or double blinded. This can be understood differently by the community and can even be misinterpreted. A story is told of a village chief who informed his community that "double-blinded" means that people participating in a double-blinded study will become blind in both eyes.

Sometimes, the difficulties observed during consenting process in vaccine trials derive from the complexity of the vaccine itself, the design of the trial, and the number of different visits, vaccinations and blood draws that need to be explained to the potential participant. Due to international requirements and the complexity of science and trial procedures, the informed consent forms are usually long and they include vast information to be absorbed in a short period of time. The clinical trials that I have been involved used ICFs that were 5 to 14 pages long. Imagine a consenter sitting with a mother and a baby (e.g., 6 weeks – 17 months old) trying to read and explain to her a 10-page long and complex document. She has little or no education, there are more children left alone at her home and plenty of housework. Is she able to fully concentrate on the strange and complex concepts that are described on so many pages?

Our consenters are trained to make the consenting process as appropriate to the potential participant's level of education and as engaging as possible so that the mother (in this example) is able to grasp the main requirements and benefits of the trial. The staff members are taught not to make a potential participant feel obliged to consent to avoid loss of service, care, treatment or to overstate benefits and understate risks of the trial. But even for the consenter there are challenges. The time the consenter can spend with each individual potential participant is limited. Some trial protocols indicate the number of participants to be enrolled within a specified time period. Therefore, the time allocated for the consenting process has to fall within the protocol design structure and it has to fit within the potential participant's schedule. For both sites (the mother and the consenter) the time is a challenge; the more time there is available to spend on discussing the study and its requirements the more competent choice the potential participant can make in regards to participate or not participate in the trial. The better the quality of the consenting process the most likely the potential participants will agree to take part in clinical trials on the understanding that they are not exposing themselves to unreasonable risks.

Another challenge related to the consenting process that has been experienced in most recent vaccine trial is the ICF amendments,

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addenda, and re-consenting activities. When a clinical trial is long, lasts for 4-5 years, the informed consent form evolves. There might be errors noticed due to mistakes in translation of ICF, typographical errors, or changes must be made due to protocol amendments (e.g., long storage of specimen samples is added), the ICF has to be again approved by the IRBs/ERCs and the participants must be re-consented. The reconsenting is often confusing to the participants and the concept of amendment or addendum is not very easy for them to comprehend despite thorough explanation. Nevertheless, they benefit from the continuous review if the information disclosed to them during the initial consenting process was adequate.

Do we as researchers know exactly how much a consented person understands all the complex issues discussed with her/him during consenting process? To measure comprehension of understanding is a task that brings up an ethical and logistical challenge. In my experience, the assessment of comprehension questionnaire does not help to adequately measure participant's understanding of the study. The administration of the questionnaire added significant amount of time to the already long and tiring consenting process and reduced the time available for answering potential participant's questions and time for open discussion. Also, especially in trials involving participants from rural settings, the questionnaire format was perceived as a test and had intimidating effect on potential participants.

Transport reimbursement and free medical care

Is it reasonable to provide reimbursement to participants when they come for protocol-defined visits or is it coercion or undue inducement?

It is important to recognize the technical difference between coercion and undue inducement.

Curtis L. Meinert in his Clinical trials dictionary: terminology and usage recommendations, 2nd ed., 2012, say: "Part of the responsibility of IRBs is to ensure informed, uncoerced consents. Coercion is consent motivated by payments or rewards presumed to have potential of causing a person to overlook associated risks in order to obtain the offered payments or rewards."

But Angela Ballantyne from Yale University Interdisciplinary Center for Bioethics points out that coercion is a threat to make someone worse off unless they comply with a given demand. In the context of research ethics, coercion is actually quite rare. Undue inducement, by comparison, occurs when the reward offered to potential research participants is so great that it undermines the participants' ability to rationally weigh the costs and benefits of research participation.

I would say that conducting clinical trials in rural areas of developing countries brings to the surface the issue of undue inducement rather than coercion. If clinical trials are conducted in rural settings, among populations of low economic status, the participants and families are struggling financially and the medical care available to them is often far from their homes and not always sufficient. Therefore, any payment or reward that would be provided for participation in the trial could be considered as undue inducement. The IRBs/ERCs review the amount of money for transport reimbursement proposed in the site specific protocol and the principle is that they should not be too much to be viewed as undue inducement. It is a challenge to come up with an amount that is satisfactory to all study participants. For some parents who stay further away from study clinics, the amount is not enough to cover travel to the clinic nor does it change when the public transport fare increase.

In many trials, medical care is provided free-of-charge to all study participants when they fall ill during their participation in the trial. In Kenya, trials provide medical care as per the Ministry of Health Guidelines on standard of care. The care that is given to study participants is of higher quality compared to care in the public health sector due to challenges that face this sector. In addition, the participants are visited at home with drugs delivery and inquiries on participant's health, hospitalizations are being covered, and mosquito nets or other commodities are being provided. One could question if these services could be called undue inducement. Debate could be raised, but the bottom line is that without providing these services, most clinical trials could not be conducted in developing countries, and the possibility of improvement and saving of human lives would not be possible.

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Protocol and moral responsibility

In clinical trials work, the protocol provides guidelines for study implementation. The procedures and all activities must be strictly adhered to and the standard of medical care should follow the guidelines of the country were the trial is conducted. However, it is sometimes difficult to follow the protocol guidelines and this can pose a challenge. For example, in a study that requires delivery of drugs to the homes of a study participant and the protocol clearly states that drugs can only be handed over to a parent or legally acceptable representative. Picture the following scenario. A field worker delivers medication to a very sick 3-year old child who is participating in a study. He finds there is no adult in the compound but only an older sibling who is 7 years old. The child is very sick and needs the medication right away. Should the drug be given to the baby by the older sibling, by the field worker, or shall the drug wait for the parent to return home? Another moral dilemma related to the protocol is patient care after the study ends. It is expected that the study participants will revert to the routine medical care available in public health facilities. There have been examples of former study participants' poor adherence to drugs, clinic visits, and of general decline in their health after the completion of a clinical a trial. What would be a good solution? Contacting study facility with information on these individuals could be deemed as disclosure of study participation and contacting the participants after a study has ended is against the study protocol and could require ERC/IRB approval.

Other challenges

Age verification

Age verification of trial participants or their guardians in Kenya is sometimes impossible due to lack of national identification cards, birth certificates, or other valid documents that states the date of birth. This is especially an issue in many developing countries. Currently, self reported date of birth is used in many trials but better ways of age verification are needed.

Participant/guardian identification

Identification of participants is sometimes a challenge especially in pediatric clinical trials. In some studies, photographs of babies participating in the study are taken at enrollment and parents/guardians are provided with ID cards which includes the child's picture. If the study duration is 3-5 years, the baby grows and the photo ID is not valid anymore. Often parent/guardian loses the ID or forgets to bring it for protocol-defined visits. Given that medical care and all the drugs are provided free-of-charge, some parents/guardians bring to the study clinic a sick child that is not a study participant and request treatment pretending that the child is a participant. Clinical trial personnel need to be aware of this challenge and put in measures to ensure that only study participants are followed up for the entire duration of the study. The consequences of not doing this could be dire, including collecting data that is not valid or compromising the safety of a study participant.

Establishment of Guardianship

Guardianship has important legal implications and in clinical trials, this needs to be established and documented. In a country where the concept of legal guardianship is not well grounded and extended family members take care of children when the parent(s) are not available due to death or travel outside the study area for an extended period or for various other reasons, establishing guardianship is not an easy task. There is need, therefore, to use methods such as questionnaires that capture pertinent information on the relationship between a participant and the person accompanying her/him and monitor change of guardianship as accurate as is logistically possible during the trial.

Conclusion

Conducting high quality clinical trials is time consuming and an expensive undertaking. Often, the timelines for completion of various steps in clinical trial implementation and reporting results are tight and pressure to complete the trial in the shortest time, with limited budget, and limited number of personnel is high. In my experience, clinical trials in developing countries are conducted with good ethical standards and despite poor infrastructure and the challenges described, the rights and well-being of trial participants well protected. The ethical challenge though applies to the staff that works on those trials. Often the tasks of patient care (including lab and pharmacy), field visits, data management, and huge amount of paperwork are being done by insufficient number of overworked staff lacking time for quality training, re-training and job security after the trial is completed.

Further reading:
Curtis L. Meinert. Clinical Trials: Design, Conduct, and Analysis. Oxford University Press

Research Ethics Support and Studies at the KEMRI-Wellcome Trust Programme

A contribution from the Community Liaison Group and ethics researchers at the KEMRI-Wellcome Trust Programme.

There are many efforts at the KEMRI Wellcome Trust Research Programme to support ethical conduct of all health research, including clinical trials, but here we discuss two aspects that might be of interest to others. The first is the work of the Community Liaison Group (CLG), and the second is the research conducted by members of the Health Research Ethics (HRE) Group.

The HRE group's work often draws upon and feeds into the CLG group's activities, but the two function quite differently. The CLG is a set of research support activities – rather like administration or IT – designed to strengthen all studies conducted by the research programme. On the other hand, the HRE is a more typical set of studies albeit with sometimes with important implications for how research is conducted by all programme researchers. All of this work is additional to following the institutional and national requirements and processes aimed at supporting ethical practice in health research, including seeking scientific and ethical review of all studies locally and nationally (and where appropriate externally), and establishment for trials of Data Safety and Monitoring Boards.

What is the Community Liaison Group (CLG) and how does it function?

A key challenge for all researchers, including those conducting clinical trials, is ensuring that there is mutual understanding and that there are strong, honest and supportive relations between staff and local residents. This is the responsibility of the CLG at the KEMRI centre in Kilifi.

The CLG comprises of a group of six facilitators, and a Community Liaison Manager, supported part time by two data entry clerks, four fieldworkers, and three researchers with an interest in research ethics. The team develop and implement annual plans for community engagement activities in the programme, which can be broadly divided into programme-wide community engagement, and project-specific engagement activities.

Programme wide community engagement focuses on the 260,000 people living within the Kilifi Health Demographic Surveillance (KDHSS) area. It includes information sharing on what research is and how participants' rights are protected in research, and information on new studies. It also includes consultation with community representatives (chiefs, leaders, and typical community members) on planned or on-going research or research policy; and feedback of research findings. These activities happen independent of individual studies, through large and small scale community meetings or barazas, regular meetings in other settings in the field (for example schools, health facilities or chief's offices) and open days and workshops at the research centre.

Study specific community engagement. Programme guidelines have been developed to support study teams to design appropriate community engagement plans for each study. CLG members sit on a Community Engagement Advisory Group set up for each study that requires community engagement, advising on activities to conduct and making sure that issues raised through interactions with community members are discussed with key stakeholders at the Programme and externally where appropriate. Study specific community engagement takes place throughout and after completion of studies, and can link with programme wide engagement where appropriate. Having CLG members involved with all community engagement is aimed at

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Members of the Community Liaison Group (CLG)

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ensuring that all activities and information sharing is properly coordinated; minimizing confusion and unnecessary repetition.

Hearing views and concerns of typical community members. For both programme wide and study specific community engagement activities, we have established a network of KEMRI community representatives (KCRs) as an additional channel of interaction beyond the more formally recognised community leaders and gate-keepers such as chiefs, village elders and other opinion leaders, and beyond the institution's more population specific community advisory board (CAB) for HIV studies. The network of 170 KCRs are intended to be typical of the general communities resident in the areas where much research takes place, as opposed to being expected to speak on behalf of the community. In an effort to ensure that KCRs come from a specific geographic area and are aware of ideas and concerns across the area as well as being accepted by the people within it such representatives are elected by local residents.

Acting on community views and concerns through guidelines and training. Issues raised in interactions with community members are considered and acted upon through regular feedback to KEMRI-Wellcome Trust Programme managers. Managers have approved internal guidelines on community engagement, and new templates for consent forms that cover (inter)national and local priorities and concerns. The programme and researchers also support training in communication and ethics for staff who communicate with potential participants about research. We recognize that this staffs are central to implementing research ethics guidelines in practice on the ground.

Recognising the Ministries of Health as 'key communities' to engage with. When developing all community engagement plans at the programme, we pay particular attention to the health facility staff and managers who are often key to ensuring that studies take place, and to responding to research findings.

Please feel free to contact us if you would like to see our community engagement guidelines. Any comments and ideas for any of our work would also be much appreciated.

The Health Research Ethics Group – Examples of recent and planned studies

Another key challenge for all researchers, including those conducting clinical trials, is understanding what the ethical issues faced on the ground are, and what their responsibilities are in these situations. The goal of the research ethics group in the KEMRI-Wellcome Trust Programme is to support the development and implementation of locally appropriate and 'ethically sound' research through conducting research on experiences and views on ethical issues from 'the field', and – in some cases – moving beyond this more descriptive work to identify researchers' and institutions' responsibilities in different situations, and the bases for these responsibilities.
At the root of much of our work are the following ideas:

- "the ethics of human subjects research may be universal but is at the same time deeply particularized, so that what autonomy or informed consent or even benefit and harm means depends on the circumstances" (p921) (King, cited in Quinn, 2004).
- "Current guidelines and regulations are an inadequate response to the complex, often unpredictable and ever shifting ethical dilemmas facing researchers in the field" (Mitchell, Nakamanya, Kamali et al., 2002).

There are a number of health systems researchers who conduct research under this theme. Many researchers are also conducting research in other health systems themes, as well as in research ethics, and although the research group is separate from CLG, there are strong links between the HRE group and CLG: HRE includes (participatory) action research on on-going community engagement activities; and there is often a need to change community engagement activities identified through ethics research.

The health research ethics studies that are being conducted could be grouped in many different ways, but one way is to consider studies related to the overlapping areas of consent, community engagement and benefit sharing. Below we give some examples of recent or on-going studies in each of these areas, each of which raise what we believe are important issues and challenges, and recommendations. We hope in future to share

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more detailed research findings with readers of this journal.

Consent studies. Consent is a core ethical requirement for much research, and it is often described as the central plank in research ethics. However it is recognized that there are challenges everywhere in the world with consent processes, and these challenges can be particularly accentuated where there are strong inequities in resources, information and power between researchers or research institutions and research communities. We have therefore been, and continue to be interested in documenting, examining and reflecting on practice for different studies and contexts. Two examples of recent studies, One is Dorcas Kamuya's recently completed PhD work on fieldworkers where one finding was the moral dilemmas the fieldworkers face when they encounter 'silent refusals' i.e where a participant does not say 'no', but dodges follow-ups and gives "credible" reasons for not making appointments repeatedly (Kamuya et al., 2013a). Reasons they might do this is to be polite; to safeguard important relations within their households (for example with the husband in the case of mothers who do not agree with a husband's decision) and with researchers (even if researchers reassure them that they are free to make their own decision. Another reason for silent refusals is for participants to participate in studies on their terms; so they continue to access to study benefits while at the same time avoiding aspects of studies they are not keen on. Another recent study looked at trial and participant perceptions of the assent procedures for an emergency fluids trial (Molyneux et al., 2013).

Community engagement (CE) studies Engaging communities can provide insights into how best to tailor consent to context and community information giving can be an important component of consent processes. However CE has far greater potential value than simply supporting consent processes. Not only can CE have other forms of instrumental value, it can also have intrinsic value, for example as a means showing respect to research participants and their communities. Although CE is increasingly promoted in health research, the meaning of the term, as well as the way in which it is best implemented in practice,

Members of the Health Research Ethics Group

are under-researched and contested. The picture becomes even more complex when we broaden the ideas of community engagement to be public engagement, or engagement with other research stakeholders. Here the ethics of collaborations and partnerships is of interest. In a Lancet commentary(Newman 2006) observed that:

"…it seems curious that we invest millions of dollars in product development, clinical training, design and building of facilities, etc., but often leave vital processes of community engagement largely to trial and error."

We have already, and are continuing to conduct, studies that look at specific mechanisms or groups that researchers engage with in research (for example Kamuya et al. 2013b, and Angwenyi et al, 2013) and have documented and commented on engagement for specific types of studies (Gikonyo et al. 2010, and Marsh et al., 2010). Future research will focus on types of studies where more standard forms of community engagement might be particularly complex or contested, including for example studies involving Most at Risk Populations, emergency research in large urban communities and health systems research.

A particular interest with regards to community consultation is how to ensure there is adequate depth to discussions. Future research will continue to build on initial studies by Marsh et al (see another contribution to this journal), which have developed a 'deliberative approach' to ethical analysis. Here, discussions with

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community representatives involve probing participants and their reasoning based on reviews of ethics literature as well as previous empirical work.

Benefit sharing studies: In our centre, we do not generally consider the distribution of benefits as a CE activity or goal of CE in and of itself. Benefit sharing and in particular the provision or strengthening of health services for research communities (including ancillary care) is crucial to facilitating ethical research, and new or different types and levels of benefits for individuals and communities may be implemented on the basis of community members' recommendations made in engagement activities. However, benefit sharing and ancillary care can be considered separate but related issues. Current studies in this area include documenting research staff and other key research stakeholder views on benefits and payments for different types of studies. We are interested in tackling the paradoxical dilemma described by Macklin (1989) as 'offer participants too little and they are exploited, offer them too much and their participation may be unduly induced' (Macklin, 1989), and more specifically in developing guidelines for our programme to supplement national and international guidelines. We are currently conducting an in-depth community consultation on the topic and plan to submit our internal guidelines to the national ethics review committee for comment and inputs when we have a draft we can share.

You can read more about these studies in the following publications:

1. Angwenyi V, Kamuya D, MwachiroD, Marsh V, Njuguna P, and S Molyneux (year). Working with Community Health Workers as 'Volunteers' in a Phase III malaria vaccine trial: practical and ethical experiences and implications. Developing World Bioethics, in press.

2. Kamuya DM, Theobald SJT, Munywoki P, Koech D, Geissler PW, S Molyneux (2013a). Evolving friendships and shifting ethical dilemmas: fieldworkers? Experiences in a short term community based intensive household study. Developing World Bioethics, in press.

3. Kamuya, DM, Theobald SJ, Munywoki PK, Koech D, Geissler WP, S Molyneux (2013). Engaging communities to strengthen research ethics in low-income settings: experiences and lessons from setting up a network of community representatives in a busy research site. Developing World Bioethics, in press.

4. Marsh VM, Kamuya DM, Mlamba A, Williams T and Molyneux S (2010). Experiences with community engagement and informed consent in a genetic cohort study of severe childhood diseases in Kenya. BMC Medical Ethics 2010, 11:13doi:10.1186/1472-6939-11-13

5. Molyneux, S., Mulupi, S., Mbaabu, L., & Marsh, V. (2012). Benefits and payments for research participants: experiences and views from a research centre on the Kenyan coast. BMC Med Ethics, 13, 13. doi:10.1186/1472-6939-13-13

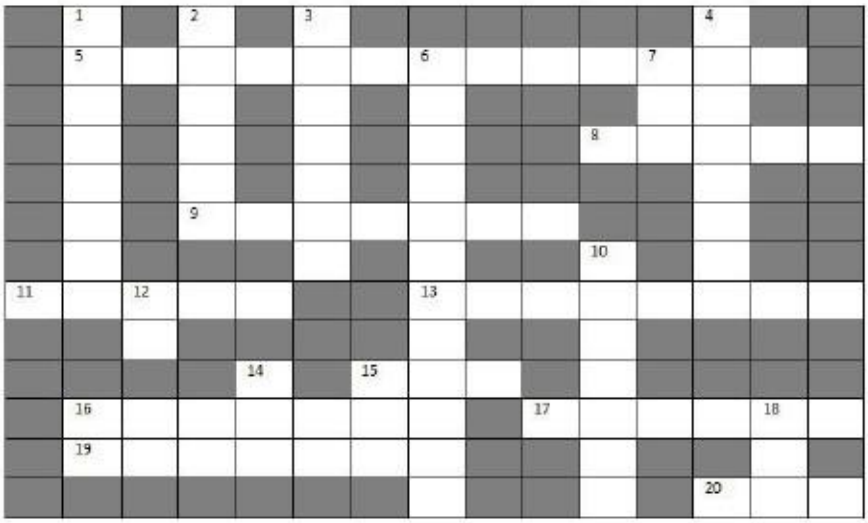
6. Molyneux CS, Njue M, Boga M, AkelloL,Olupot-Olupot P, EngoruC, Kiguli S, K Maitland (2013). The words will pass with the blowing wind': staff and parent views of the deferred consent process with prior assent used in an emergency fluids trial in two African hospitals, PLOS One, in press.

7. Peter Newman: The Lancet, Volume 367, Issue 9507, Page 302, 28 January 2006

8. Boga, M., Davies, A., Kamuya, D., Kinyanjui, S. M., Kivaya, E., Kombe, F, Lang T, Marsh V, Mbete B, Mlamba A, Molyneux S, Mulupi S and Mwalukore, S. (2011). Strengthening the informed consent process in international health research through community engagement: The KEMRI-Wellcome Trust Research Programme Experience..PLoS Med, 8(9), e1001089. doi:10.1371/journal.pmed.1001089

9. Kamuya DM, Marsh V, Kombe F, Geissler WP and S Molyneux. Engaging communities to strengthen research ethics in low-income settings: selection and perceptions of members of a network of Representatives in coastal Kenya. Developing World Bioethics, in press.

ETHICS CROSSWORD PUZZLE



Across

5. Process of assigning trial subjects to treatment or control groups using an element of chance in order to reduce bias
8. The location where trial-related activities are conducted are called _____sites
9. An individual or organization which takes responsibility for the initiation, management and/or funding of a clinical trial
11. A double-_____study is a clinical trial in which study participants and investigators are kept unaware of treatment assignment
13. To participate in a research study one should voluntarily provide _____consent.
15. Any untoward medical event that occurs after a participant has received any treatment dose and whose outcome is life-threatening, requires hospitalization or prolongation of hospitalization, or results in disability/ incapacity or death (abbrev).
16. An international set of guidelines or statement on how to report the findings of a clinical trial
17. What the members of an ethics committee does to a study protocol
19. An inert pharmacological substance received by or a sham procedure performed on the control group
20. The international standard for the design, conduct, analysis and reporting of clinical trials that provides assurance of the data credibility and accuracy and protects the confidentiality of trial participants (abbrev).

Down

1. A document that describes the objectives, design, statistical plan and organization of a trial
2. The process of enlisting an eligible potential study participant.
3. The trial group that does not receive the experimental treatment
4. To oversee the progress of a clinical trial and ensure it is conducted according to protocol and applicable regulatory requirements
6. A person responsible for the conduct of a clinical trial at a trial site
7. Intellectual property rights (abbrev)
10. The act of voluntary confirmation of willingness to participate in a research study
12. Investigators' brochure (abbrev)
14. The KEMRI committee that reviews the scientific content of proposals (abbrev)
18. The KEMRI committee that performs ethical review of proposals (abbrev.)

NB: ***There were no submissions received for the Issue's crossword. A prize will be awarded for the two most complete submissions for this Issue's crossword sent to ddrt@kemri.org .***

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