SIGNA VITAE 2016; 12(1): 14-18

Evolving from Past to Future: Facilitating SMART research

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ABSTRACT

In clinical research, there has been an increasing need to titrate ethical, legal and insurance requirements to the type of study, so that higher-risk research receives necessary and appropriate detailed attention, while low-risk studies can proceed more rapidly.

Spontaneous Medically Advantageous Research Trials (SMART) are non-profit studies that carry minimal or no risk to patients. This type of investigation, however, is currently hampered by the fact that, in many hospitals and jurisdictions it has to undergo the same bureaucratic procedures and safety assessments as high-risk, for-profit studies. We strongly believe that such practice of scientific research assessment should be radically modified. We advocate a new, specific research category for SMART investigations that grants them a preferential route from conception to ethics assessment to execution. In addition, we argue that such low risk studies assessing common, often not evidence-based applied treatments or investigations should in fact be a mandatory component of modern medicine. All clinicians, scientists, patients, patient associations, politicians, scientific associations and common citizens should be involved in this process, as they all play a crucial role in its evolution and success.

We contend that modern medical research and entire health systems should transition to a novel model of healthcare system where SMART execution is embedded into daily practice, in order to minimize anecdotal practice and maximize evidence-based practice.

Key-words: no profit study, medical research, ethical committee, progress

"It is not the strongest or the most intelligent who will survive but those who can best manage change." Charles Darwin

We contend that, in 2015, the Helsinki Declaration and Ethical Committees are, at times, indirectly disadvantaging patients. In this article we try to explain the reasons why and the possible solutions.

One of the objectives of modern health care is to create a learning health care system. The Institute of Medicine defines such a health care system as one "in which knowledge generation is so embedded into the core of the practice of medicine that it is a natural outgrowth and product of the healthcare delivery process and leads to continual improvement in care". (1)

Research and clinical practice, however, have historically been clearly two distinct areas of medical science: by contrast, the learning health system emphasizes the fundamental need to integrate these two aspects of healthcare into one whole. (2)

The model of the learning health care system is, of course, in line with the cornerstone of human research ethics, the 1964 Declaration of Helsinki, (3) and its revisions and clarifications.

This concept encompasses a set of ethical principles regulating human experimentation developed by the World Medical Association. The fundamental principles are the respect for the single patient, the right to self-determination and the right to make informed decisions regarding participation in research, both initially and during the course of the study. While there is a continuous need for research and improvement, the subject's welfare must always come before the interest of science, and ethical considerations must precede and guide laws and regulations. The investigator's primary concern must be the safety and well-being of the subject or volunteer.

Faden et al. recently proposed a Common Purpose Framework (4) aimed at promoting the implementation of the model of a modern health care system into clinical reality. This framework is built on the traditional principles of clinical and research ethics, but at the same time the system is also conceived to guide activities where research and practice are integrated to enable rapid, systematic, and effective learning.

The proposed Common Purpose Framework comprises seven moral precepts (4): a) respect the rights and dignity of patients; b) respect the clinical judgments of clinicians; c) provide optimal care to each patient d) avoid imposing nonclinical risks and burdens on patients; e) reduce health inequalities among populations; f) conduct

activities that foster learning from clinical care and clinical information; g) contribute to the common purpose of improving the quality and value of clinical care and health care systems.

The first six obligations directly involve researchers, clinicians, health care administrators, institutions, and insurers. The seventh, on the contrary, invites patients to participate in some learning activities that are integrated in their clinical care.

In such a health care system, transparency to patients is obviously crucial. However, in this sense, for example, patients might not be routinely informed about each learning activity, provided that these are seen not to carry risks for patients that are greater than the risks associated with standard. On the contrary, patients would always be informed, and their consent would always be sought, whenever a learning activity might impact on the quality of care or its outcomes. (4) This concept is extraordinarily modern and challenging, but still far from being a clinical reality.

Despite this strong theoretical basis, the evolution of contemporary health care into a learning health care system is just beginning, and many different health care systems in different countries are organized and regulated in their own way.

We truly believe that, in light of the preventable harm, waste, and uncertainty that affect clinical effectiveness in health care, all efforts to enhance and accelerate learning are extremely important. The first step towards implementing such a learning health system is to define its core ethics and its specific moral obligations.

Some ethical issues are crucial and yet extremely debated. The local Ethics Committee's decision might sometimes contradict national laws, but the power of Ethics Committees on the development of clinical trials has never been formally challenged. There has not been and there is no evidence-based assessment of their performance, the reproducibility of their judgments, and their accuracy in making such judgements.

A major issue in this regard is, for example, whether informed consent should be always and indiscriminately required. We are fully aware of the pivotal importance of informed consent, but we believe it should not be indiscriminately applied especially where interventions or measurement are part of common or routine care.

Faden et al. further analyzed this aspect in a recent article published in the New England Journal of Medicine (5) specifically addressing the role of informed consent in comparative effectiveness research (CER) studies. The authors emphasize that some randomized CER studies may proceed with a streamlined consent process and others may even not require patient consent.

While we are fully aware that the current regulations on this matter are partially justified by past episodes of lack of observance of patients' rights, we also believe that we have evolved and now face new, even opposite challenges: regulations and ethical requirements of research must keep up to date, or modern research will be adversely affected, improvements in care will be delayed and patients will be ill-served.

We argue that current consent and oversight practices too often overprotect patients from research that has little direct effect on what is relevant for them and yet may lead to improved care over time. By doing so, in addition, they may deprive them and their next of kin and future patients of better care.

The recent "Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014" addresses this issue, together with many other critical aspects of modern scientific research, but many problems remain and still warrant clarification. (6)

From our point of view, the power of local ethical committees may even have detrimental effects: by delaying and impeding SMART studies they may indirectly adversely affect patient outcomes. In many jurisdictions, impediments, discussions, delays and costs due to local ethical committees are progressively worsening. Therefore, an unambiguous legislation issued by a centralized referral institution is strongly recommended.

Another hot topic is non-profit research, which is a major driving force of medical progress. If non-profit studies are independent from the influence of pharmaceutical companies, they are in fact conceived and performed in the interest of patients, and lead to improvements in patient care.

In spite of this, approval of such studies is increasingly difficult all over the world. The bureaucratic and safety assessments they have to undergo are the same as those of pharmaceutical and for-profit studies, even when they are evaluating and comparing, for example, drugs that have been used in clinical practice for years and are prescribed according to non-evidence based physician preference or minimal differences in drug doses. In our opinion, bewilderingly, sometimes local ethics committees and the need for informed consent impede this type of study often more than with pharmaceutical drug trials.

Sponsored pharmaceutical studies are often characterized by a relatively high risk/great benefit dichotomy for patients, and their expenses for insurance, ethics committee and monitoring are generally fully covered by the commercial sponsor itself. Conversely, spontaneous non-profit studies, even when they put patients at negligible risk (no greater on any estimate than the risk associated with being exposed to standard care), often undergo the same insurance, and bureaucratic requirements as sponsored studies, but without financial backing by a sponsor. This is another major limitation to the development of non-profit studies. The requirements of the ethical committee vary greatly from country to country across the continents. Some national realities show a very modern attitude toward research, but on the contrary in some contexts the ethical approval process strongly jeopardizes research due to the prolonged time required (up to months) for the approval of the studies. For example, continuous requirements of further specifications and information regarding the study are asked of the researchers because most of the members of the ethical committees are not medical doctors dealing with patients.

Furthermore, in our experience, many local ethics committee evaluations require the payment of a fee (the amount is generally hundreds of Euros), and specific insurance has to be taken out even for non-profit no-risk studies (thousands of Euros). Excessive monitoring and the need for dedicated personnel to follow the bureaucratic procedures with the ethics commit-

tees, cause further considerable expenses. Financial resources are not enough and grants are limited in number and budget. The resulting time delay is impressive. Obstacles and requirements paradoxically increase when an initially single-centre, not-for-profit study aims at involving other centres, even though multicentre studies are those that provide the strongest scientific evidence.

Today, with the entire world potentially connected and synchronized, it would be possible and relatively easy to perform innumerable trials on many every-day aspects of clinical practice, refining small details that, all together, would incrementally improve patient care as a whole. The direct impact on patient outcome and indirect reduction of medical expenses would likely be immensely beneficial to both patients and society on a global scale.

Based on these observations, we have developed a new concept of non-profit, negligible risk research. We identify the above-mentioned studies with the acronym SMART, which stands for "Spontaneous, Medically Advantageous for patients Research Trials (SMART)". The characteristics of SMART studies are summarized in table 1. The term SMART includes any study that carries negligible risks for patients, does not study new drugs or devices and is not in the interest of pharmaceutical companies. At the same time, the information that might be delivered by these studies is fundamentally important for the patient community worldwide.

Table 1. Profile of the Spontaneous Medically Advantageous Research Trials (SMART) concept.

Characteristics	**Description**
Nature of the study	Non profit, spontaneous.
They offer the best consensus-established available standard treatment.	
Risk for patients	No additional risk (only those arising from standard clinical practice)
Benefits for patients	Significant
Benefits for society	Significant
Benefit for future patients	Significant
Need for informed consent	According to the study
Information provided	Relevant
Ethics Committee expenses	None
Insurance	None (only the one already offered for standard clinical procedures)
Monitoring expenses	None (simple, clinically relevant endpoints that could be obtained by standard electronic databases)
Ethical requirements	Written approval from at least 10 independent physicians with at least 20 papers already recently published in indexed journals and working in at least 10 different nations in at least 3 different continents. Final approval by a Central Ethical Committee only.
Visibility	Uploaded on an international on-line database

We would also like to stress the importance of the Hawthorne effect, which plays a relevant role in these kind of studies. (7-11) The Hawthorne effect (also referred to as the observer effect) is the phenomenon whereby individuals improve or modify an aspect of their behavior in response to the awareness of being observed. The original "Hawthorne effect" study suggested that the novelty of being research subjects and the increased attention from such could lead to temporary increases in workers' productivity. Translated into the context of current scientific research, this means that the simple fact of being research subjects and the increased attention from such, may improve patients' outcome. The positive influence that clinical trials may have on hospital survival was also directly posited by us in a recently published editorial. (12) In this work we tried to identify the factors contributing to the extremely low perioperative mortality (0.3%) observed at our Institution when compared to published European standards.

All researchers strongly agree that evaluation by an ethics committee, with or without the need for written informed consent, should be mandatory for high risk studies, for those related to pharmaceutical companies and to new drugs or devices, but lower costs and less bureaucracy might be considered appropriate for SMART type-investigations.

The ethics and bureaucratic requirements and costs should be completely reshaped for SMART's, allowing a bigger number of institutions and colleagues to share their data with the scientific community.

Our aim is to promote the evolution of the Health care system into a Learning health care system. We think that publicizing the concept of SMART research is a crucial step towards this objective.

We challenge the one-size-fits-all approach in clinical research bureaucracy in favour of a tailored approach, based on the effective likely risk to which each patient is exposed due to his or her participation in the

study. We are aware that it would be unadvisable and unethical for patients to pay a fee for access to research trials. At the same time, inclusion in a SMART study should often be considered a privilege and not an added risk, and both national and local health systems should support centers performing SMART type studies rather than centers that do not undertake such studies.

Such a strategy would open new revolutionary and challenging horizons in clinical research. Furthermore, this new approach to research would not be limited to a specific sector, as it is by definition multi- and inter-disciplinary, and can be applied to all aspects of modern biomedical research. Revolutionizing current scientific research practice is key to facing the above-mentioned problems of modern scientific research. Examples of studies which may be considered SMART include: observational (non-interventional) protocols, either retrospective or prospective, audits, improvements in clinical practice studies, before-and-after studies of practice changes, spontaneous randomized and cluster cross-over randomized trials of widely used and currently widely applied therapies.

These studies provide crucial information for scientific progress.

A list of examples of modern trials that also fulfil the criteria of SMART studies is shown in table 2.

Table 2. Modern trials which fulfil the criteria for Spontaneous Medically Advantageous Research Trials (SMART) studies.

Project Title	Promoting country/scientific association	Started in
REstrictive versus LIbEral Fluid Therapy in Major Abdominal Surgery	Australia	2014
The BALANCED Anesthesia Study A prospective, randomized clinical trial of two levels of anaesthetic depth on patient outcome after major surgery	Australia	2014
Randomized Isoflurane and Sevoflurane Comparison in Cardiac Surgery (RISCCS)	Canada	2014
Early Non-invasive Ventilation Outside the Intensive Care Unit	Italy	2014
Volatile anesthetics to reduce mortality in cardiac surgery. A multicentre randomized controlled study.	Italy	2012
International Prospective Observational Study of Mechanical Ventilation Discontinuation Practices. IOSwean.	Canadian Critical Care Trials Group	2012

Furthermore, due to the inherent nature of SMART research as previously defined, we believe that specific, additional insurance and other bureaucratic requirements should be waived. The need for written informed consent will vary according to the type of study.

In order to guarantee that the principles of Helsinki are respected, we suggest that some requirements for SMART trials be fulfilled.

Observational studies will be performed without specific ad hoc written consent and without the need for approval by the local ethical committee. At the time of submission of the study as a scientific article, peer reviewers will evaluate the study, and they may require further ethical information or evaluation by the local ethical committee when deemed necessary. This process will be appropriate for all types of observational studies, thus including retrospective studies, observational studies collecting normally discarded material (urine/feces) or blood, prospective observational studies collecting survey and questionnaire data, single center before-and-after studies.

Moreover, when an author wants to perform an interventional SMART study (including multicenter cluster randomised controlled trials (RCTs), multicenter stepped wedge design studies, pilot change of practice studies, …), the study protocol might, for example, be required to:

Receive written support from at least 10 independent physicians working in at least 5 different nations in at least 2 different continents. These physicians could have experience in research activity (at least 20 papers already published in indexed journals), and should obtain all data that they need to evaluate the work before giving their written approval.
Be uploaded on an international online database.
Offer all the patients the best available standard treatment as control therapy (as agreed by the above clinicians).
The need for a specific written consent for SMART interventional studies is not established a priori. The authors of the study protocol will evaluate whether an ad hoc informed consent is needed for their study. The 10 independent physicians who will eventually approve the paper will evaluate the study protocol and confirm the proposal or suggest changes to the study protocol concerning this aspect.

Finally, a Central Ethics Committee should confirm that the protocol is SMART. All the studies will be accessible online via a website, together with the written approvals (with signatures) by the 10 physicians. In this way, transparency towards medical colleagues and patients would be ensured. This procedure would be fully standardized, in order to guarantee that SMART research by worthy researchers all over the world is not delayed.

In order to further ensure that this simplified procedure for SMART will not carry damage to patients, we also imagine a multiphase process.

Initially, this procedure would be implemented and tested for a limited period of time. This first phase may last 3 years, and then an analysis of all SMART processes performed will be carried out, in order to identify their impact on patients, the ben-

efits, and the potential critical issues which should be addressed. After this rational and scientific justification of SMART interventions, the second phase would begin, that is to say, the SMART process will become routine practice with no time limit.

SMART research is not only a new way of doing research: it is a new mind-set. For this reason, great efforts should be made to promote, spread and explain this approach all over the world. Politicians, patients, and associations of patients must all be protagonists. Scientists will be directly involved, as we will organize consensus conferences on SMART research to promote this concept and to address specific issues. Campaigns to promote SMART research should be set up through the web. A preferential route for the presentation of SMART abstracts at congresses and the publication of SMART papers should be guaranteed. As the direct involvement of patients is crucial for success, SMART activities should be made public using lay media (televisions, newspapers, internet) and members of the public should be involved in the development process.

The participation of patients should be further facilitated using technology and the patients' preferred instruments. For example, the follow-up of studies could be performed by SMS, e-mail, or through ad hoc designed applications on Smartphones and tablets.

The potential of SMART research is substantial: it is therefore crucial that it be protected from financial issues that influence sponsored research and from the severe budget constraints caused by bureaucracy and redundant insurances.

SMART can lead the way of scientific research. It is time to write a new Declaration of Helsinki, to protect patients from not being involved in research, to widen the horizons of biomedical research, and to finally implement the transition to a learning health care system.

REFERENCES

1. Institute of Medicine (US) Roundtable on Evidence-Based Medicine; Olsen LA, Aisner D, McGinnis JM, editors. The Learning Healthcare System: Workshop Summary. Washington DC, (USA): National Academies Press; 2007.
2. Largent SJ, Miller FG. Can Research and Care Be Ethically Integrated? Hastings Cent Rep 2011;4:37-46.
3. WMA Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects. [INTERNET] World Medical Association; 1964. [Last amended in October 2013; cited on October 3rd 2014] Available from: http://www.wma.net/en/30publications/10policies/b3/.
4. Faden RR, Kass NE, Goodman SN, Pronovost P, Tunis S, Beauchamp TL. An ethics framework for a learning healthcare system: a departure from traditional research ethics and clinical ethics. Hastings Cent Rep Spec No 2013; S16-S27.
5. Faden RR, Beauchamp TL, Kass NE. Informed consent, comparative effectiveness, and learning health care. N Engl J Med 2014;370:766-8.
6. Regulation (EU) No 536/2014. European Parliament; 2014. [INTERNET][Cited on October 14th 2014] Available from: http://ec.europa.eu/health/files/eudralex/vol-1/reg_2014_536/reg_2014_536_en.pdf.
7. Parsons H. What happened at Hawthorne? Science 1974;183:922–32.
8. Sommer R. The Hawthorne dogma. Psychol Bull 1968;70:592–5.
9. Wickstrom G, Bendix T. The "Hawthorne effect"—what did the original Hawthorne studies actually show? Scand J Work Environ Health 2000;26:363–7.
10. Gale E. The Hawthorne studies—a fable for our times? QJM 2004;97:439–49.
11. Chiesa M, Hobbs S. Making sense of social research: how useful is the Hawthorne effect? Eur J Soc Psychol 2008;38:67–74.
12. Landoni G, Pasin L, Monti G, Cabrini L, Beretta L, Zangrillo A. Towards zero perioperative mortality. Heart Lung Vessel 2013;5:133-6.