Published in final edited form as:
Clin Trials. 2014 December ; 11(6): 622–623. doi:10.1177/1740774514553482.

Commentary on Vickers

Michael S Lauer, MD, FACC, FAHA [Office of the Director]
Division of Cardiovascular Sciences (DCVS), National Heart, Lung, and Blood Institute (NHLBI), Bethesda, MD

In February 1986, I was a medical intern rotating in a large teaching hospital coronary care unit. Every morning at 7 AM sharp our attending rounded with the house officers, seeing 5-6 critically ill patients who were admitted with acute coronary syndromes, sometimes with awful complications. One morning, instead of starting straight off with the patient in Room 1, she told us that she had an important announcement: *Lancet* had just published an article[1] that would "transform the practice of cardiology." I don't remember whether I believed it or wrote off her excitement to the hyperbole of an enthusiastic cardiologist, but looking back, 28 years later, her prediction was spot on.[2,3]

The article, of course, was the report of the main results of the GISSI-1 trial. Italian investigators enrolled nearly 12,000 patients whose doctors thought were having a myocardial infarction and who had no contraindications to thrombolytic therapy. Using a remarkably simple design, the investigators found that streptokinase reduced the risk of death and appeared to be safe. The trial took only 17 months to conduct, and cost less than $500,000[2] – less than the cost of a typical NIH R01 grant!

The investigators pulled off this feat by keeping their trial simple – very simple – and by integrating the trial into routine myocardial infarction care.[2] And they not only transformed the standard of practice for the care of patients with myocardial infarction, they and other mega-trialists around the world changed the way clinicians think about evidence.[4] The late 1980s and early 1990s were exciting times for a budding cardiologist – it seemed as if every few weeks we'd hear about yet another mega-trial report, a report that would take us one step closer to a clinical world in which 100% of decisions were based on high-quality evidence. It was just a matter of time.

It didn't happen. As Vickers[5], in his thoughtful commentary in this issue of *Clinical Trials* and others[4] have noted, we now find clinical trials in a state of crisis. Trials are expensive, complex, bureaucratic, time consuming, and even after all that, often end up underpowered or inadequately designed to answer real world clinical questions.[6,7] At NHLBI, we found that a disturbingly large number of trials we've funded over the past 15 years didn't even publish their main results within 2.5 years of completion; this was especially true for small trials that focused on surrogate endpoints.[8] Trialists are often unable to recruit patients on time and on budget, and this is so even (perhaps especially) for trials focusing on common

Please address all correspondence to Dr. Lauer at lauerm@nhlbi.nih.gov.

Disclaimer: The views expressed in this essay are those of the author and do not necessarily reflect those of the NHLBI, the National Institutes of Health, or the US Department of Health and Human Services

diseases. And in my world of cardiovascular medicine, a field that prides itself on being evidence-based, < 15% of active practice recommendations are based on high-quality evidence, that is evidence coming from multiple clinical trials.[9]

Vickers[5] cites a number of ongoing efforts – including the Clinical Trials Transformation Initiative and the NIH Collaboratory – and proposes four “simple methodological fixes.” Investigators should simplify trials to reduce eligibility criteria, integrate trials into clinical care, employ cluster randomization, and consider early consent. Vickers cites previous experience with all these approaches and acknowledges that sometimes they won't work. He correctly notes that there is debate about the role of research within clinical care – we are far from convincing many of our physician colleagues, the public, and policy makers that clinical care should routinely be subject to rigorous scientific inquiry.[10,11]

Vickers' four “fixes” all make sense, and are all in themselves evidence-based. What's not to like? I think there are some missing elements, so I'd like to offer a few friendly amendments.

First, and probably foremost, we must remember that the people with the greatest stake in the conduct and findings of clinical trials are patients. Yet patients are usually left out of the conversation until late in the game. We often refer to patients as “research subjects” who are asked to provide “informed consent.” It is the exception when patients are engaged early, helping investigators identify priorities, designing protocols, thinking through human safety and consent concerns, helping recruit participants through their advocacy groups, and pushing physicians to participate. We've seen some inspiring examples; a recent *New England Journal* editorial focused on the engagement of patients who enabled a landmark trial of a treatment for a rare lung disease.[12] Often we at NIH find ourselves frustrated overseeing trials that somehow can't meet enrollment targets despite studying common problems. Wouldn't it be fabulous if patients were banging on the doors, insisting that their physicians work with them to get them enrolled in large-scale practice-defining trials? Perhaps we find ourselves on the cusp with the development of the Patient-Centered Outcomes Research Institute (PCORI) Network (“PCORnet”), which has deliberately chosen to fund “Patient-Powered Research Networks” along with the more traditional “Clinical Data Research Networks.”[13,14]

Second, many observers view “clinical integration” with suspicion because they inherently disbelieve data coming from electronic health records. The electronic health record may not yet be “research ready” for routine use, but many of us are confident that it's getting there. In the meantime there is another kind of integration – integration into high-quality professional society registries that in some cases have achieved high degrees of penetration into clinical care. The “randomized registry trial” offers another opportunity to conduct large simple trials at low cost.[6]

And third, clinical integration may be difficult to accomplish because there are some stakeholders who are less than enthusiastic. Hospital administrators worry about research interfering with workflow and already challenged revenue streams. There were active groups who resisted the conduct of trials of hormone replacement therapy, bone marrow transplantation for metastatic breast cancer, stenting after myocardial infarction, and CT

scanning in heavy smokers.[15,16] I wonder whether one strategy for dealing with this comes back to my first friendly amendment – bring informed and engaged patients to the table. And not only patients, but also bring in business officials, who may not fully appreciate their stake in advancing clinical care through routine use of the scientific method.

I commend Vickers for his direct approach to the cultural barriers that impede our ability to rediscover how to design and conduct transformative trials like GISSI. With strong leadership and with extensive dialogue among all stakeholders, in particular patients and their caregivers, we could well make it happen.

References

1. Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico (GISSI). Effectiveness of intravenous thrombolytic treatment in acute myocardial infarction. Lancet. 1986; 1:397–402. [PubMed: 2868337]
2. Tavazzi L, Maggioni AP, Tognoni G. Participation versus education: the GISSI story and beyond. Am Heart J. 2004; 148:222–229. [PubMed: 15308991]
3. Yusuf S. Transforming the scientific, health care, and sociopolitical culture of an entire country through clinical research: the story of GISSI. Am Heart J. 2004; 148:193–195. [PubMed: 15308987]
4. Antman EM, Harrington RA. Transforming clinical trials in cardiovascular disease: mission critical for health and economic well-being. JAMA. 2012; 308:1743–1744. [PubMed: 23117771]
5. Vickers AJ. Clinical trials in crisis: four simple methodological fixes. Clin Trials. 2014
6. Lauer MS, D'Agostino RB Sr. The randomized registry trial--the next disruptive technology in clinical research? N Engl J Med. 2013; 369:1579–1581. [PubMed: 23991657]
7. Eapen ZJ, Lauer MS, Temple RJ. The imperative of overcoming barriers to the conduct of large, simple trials. JAMA. 2014; 311:1397–1398. [PubMed: 24715072]
8. Gordon D, Taddei-Peters W, Mascette A, et al. Publication of trials funded by the National Heart, Lung, and Blood Institute. N Engl J Med. 2013; 369:1926–1934. [PubMed: 24224625]
9. Tricoci P, Allen JM, Kramer JM, et al. Scientific evidence underlying the ACC/AHA clinical practice guidelines. JAMA. 2009; 301:831–841. [PubMed: 19244190]
10. Faden RR, Beauchamp TL, Kass NE. Informed consent, comparative effectiveness, and learning health care. N Engl J Med. 2014; 370:766–768. [PubMed: 24552325]
11. Wilfond BS, Magnus D, Antommaria AH, et al. The OHRP and SUPPORT. N Engl J Med. 2013; 368:e36. [PubMed: 23738513]
12. Ingelfinger JR, Drazen JM. Patient organizations and research on rare diseases. N Engl J Med. 2011; 364:1670–1671. [PubMed: 21410388]
13. Collins FS, Hudson KL, Briggs JP, et al. PCORnet: turning a dream into reality. J Am Med Inform Assoc. 2014; 21:576–577. [PubMed: 24821744]
14. Selby JV, Krumholz HM, Kuntz RE, et al. Network news: powering clinical research. Sci Transl Med. 2013; 5:182fs13.
15. Marshall E. A bruising battle over lung scans. Science. 2008; 320:600–603. [PubMed: 18451275]
16. Lauer MS. Commentary: Will academia embrace comparative effectiveness research? Acad Med. 2011; 86:671–673. [PubMed: 21613887]