

Embedding patient- and public health-oriented research in a national health service: the GISSI experience

Gianni Tognoni, Maria Grazia Franzosi and Silvio Garattini

IRCCS Istituto di Ricerche Farmacologiche, 'Mario Negri', Milan 20156, Italy

Corresponding author: Gianni Tognoni. Email: tognoni@marionegri.it

Introduction

In their book *Good Pharma: the public-health model of the Mario Negri Institute*, Donald Light and Antonio Maturo¹ documented the ethos, origins and development of the Istituto Farmacologiche 'Mario Negri'. One reviewer commented that the book combines 'a devastating critique of the pervasive harms of patent-driven medical research by the pharmaceutical industry with a compelling account of an alternative patient-driven, no-patent research'.²

In his Foreword in *Good Pharma*, Iain Chalmers³ notes that the mission of the Mario Negri Institute since its inception in the 1960s has been 'to do research of international quality to improve people's health, based on independent, transparent science, openly used to educate doctors and patients about how best to address their health needs'.

The Mario Negri Institute has used a variety of strategies to promote its mission. One of these is to embed clinical research within publicly orientated healthcare. This requires collaboration with the doctors providing and the patients receiving care.⁴ The philosophy underlying this element of the Institute's mission has been elaborated as follows:

Research is an expression of care. It cannot be separate, parallel or occasional (as it is for commercial testing) and yet still be clinically real. The greatest risk in clinical medicine is to dissociate care from research about how effective that care is. Yet this is what usually happens. Rather, research into treatments must be nested within practice.⁵

The principle of embedding patient- and public health-oriented research within a health service is reflected in the research done by Il Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI). GISSI's first report⁶ was selected for inclusion in the James Lind Library because of its historical importance in the evolution of fair tests of treatments. This article is

a commentary on GISSI's first trial, the way it was received, the series of GISSI trials that it initiated and a discussion of the relevance of the GISSI today.

Il Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI)

Previous articles^{7,8} have reviewed the reasons for the interest generated by the first GISSI trial.⁶ Together with the contemporaneous ISIS-2 trial,^{9,10} the first GISSI trial was considered to have made an innovative contribution to the evolution of trial methodology: it had bridged the usual gap between research and healthcare by embedding the former in the latter. In doing so, it addressed the difference between explanatory (efficacy) and pragmatic (effectiveness) trials,¹¹ as called for by Archie Cochrane.¹²

The background for this innovation had been established a few years before, outside and beyond the lively debate about the different philosophies and purposes of explanatory versus pragmatic trials.¹³ In particular, in mainly statistically oriented papers, Richard Peto¹⁴ drew attention to the need for substantially larger trials in cancer^{15,16} and cardiovascular diseases.¹⁷

A common goal of papers such as these was to stress that clinical trials were needed to compare interventions reliably in the type of patients ('populations') presenting in routine care settings, and they needed to be large enough to yield patient-important outcomes over periods of time that reflected the natural history of the conditions of interest. The first GISSI trial was the first to demonstrate that this approach was feasible. It was planned, implemented, concluded and published with dramatically innovative results over a period of only 2.5 years. More than 12,000 patients with definite or suspected heart attacks participated in the study, a sample size that was uniquely large for a treatment trial at that time.

The philosophy of this study design had been shown to fit well within usual healthcare: real-life data were collected within the routine and

heterogeneous conditions of care; the data were collaboratively controlled and centrally supervised according to agreed pre-defined quality criteria and these were shown to be as informative as the rather artefactual information derived from strictly selected ‘samples’ of patients meeting well-defined diagnoses, but not representing real clinical populations.

The innovative aim of the principles followed and promoted by GISSI had been to provide clinical experiments with a natural epidemiological framework that bridged scientific rigour and basic needs: application of these principles in practice had been achieved by a nationwide network of non-academic NHS hospitals collaborating in strict alliance with an independent research institution. For the first time, a simple-to-use, inexpensive treatment had been shown convincingly to reduce premature death after myocardial infarction (heart attack).⁶

Even before the results of the trial had been published, their importance was recognised in closing remarks at a meeting of the American Heart Association in November 1985 and in modifications of the US National Institutes of Health’s strategy on thrombolysis. Significantly, the drug regulatory authorities recognised that the available evidence supporting an old drug – streptokinase – was better than that supporting the technologically highly innovative drug tissue plasminogen activator (tPA). Although there was evidence favouring tPA in classical experimental settings, only surrogate laboratory outcomes were available.

Methodological, public health and cultural implications of GISSI’s research

The first GISSI trial has been seen as contributing a ‘revolutionary’ step forward in trial design and

execution, and it led to five further GISSI trials (Table 1).

Which of the features of the GISSI trials might reasonably be accepted as fundamental to their success? And how applicable are they in the current regulatory framework for clinical trials?

A shared perception of unmet needs: The broader cultural context in which GISSI was conceived and realised may have been the main determinant of its success. There was a shared perception of unmet needs at the core of cardiology, with many fragmented proposals on thrombolysis in the clinical and basic research literature. First, the cultural and political scene a few years earlier had led to the creation of a national health service in Italy. Second, a leading non-academic cardiologist (Fausto Rovelli, president of the Italian Association of Hospital Cardiologists) accepted the challenging proposal that an independent, non-profit organisation (Mario Negri) should consider the whole of Italy as the ‘natural laboratory’ in which to run a trial which was itself a cultural and institutional experiment.^{23,24}

Following intense and stimulating public discussions with key clinicians, the GISSI protocol was adopted as an expression of collective responsibility: it promised to produce original scientific knowledge, and to upgrade the methodological competence and the public health awareness of the cardiological community at a national level. Over a period of four months, in each of the 20 regions of Italy, the promoters of the trial were ‘on the road’ presenting, explaining and discussing what should be done to translate routine good practices into quality-controlled data collection. Participation by 90% of Italian Coronary Care Units and the completeness and quality of follow-up⁶ are testimony to the overall success of these initiatives.

Table 1. Characteristics of the six studies organised by GISSI, 1984-2007.

	GISSI-1 ⁶	GISSI-2 ¹⁸	GISSI-3 ¹⁹	GISSI-Prev ²⁰	GISSI-HF ²¹	GISSI-AF ²²
Enrollment	1984–85	1988–89	1991–93	1993–96	2002–05	2004–07
Publication	<i>Lancet</i> , 1986	<i>Lancet</i> , 1990	<i>Lancet</i> , 1993	<i>Lancet</i> , 1998	<i>Lancet</i> , 2008	<i>NEJM</i> , 2009
No centres	176	223	200	172	351	114
No patients	11,806	12,490	19,394	11,379	6975	1442
Total costs	350,000 €	4M €	6M €	4M €	20M €	3.7M €
Cost per patient	30 €	320 €	309 €	350 €	2800 €	2680 €
Regulatory approval	SK by FDA	–	Lisinopril by FDA	n-3 PUFA by IMH and EMA	–	–

GISSI: Il Gruppo Italiano per lo Studio della Sopravvivenza nell’Infarto Miocardico.

Coincidence of clinical, pathophysiological and public health objectives: A second, strictly complementary reason was that the trial was attractive and its proposed design accepted because of a coincidence of clinical, pathophysiological and public health interests and objectives. The outcome end point of mortality in so large an unselected population was also a crucial test of the hypothesised underlying cause(s) of myocardial infarction: Was there only one or several different mechanisms? Were thrombi and/or arterial spasms critical? Were there differences in treatment effects between young and old people? Was there a critical time for preserving myocardial tissue? The protocol for the trial addressed these questions, which had taken up years of ‘explanatory’ investigations and controversial debates worldwide. For the first time, the trial provided robust answers to most of these issues. The experience and the acquisition of an identity among the Italian cardiologists had shown how care and research could be combined to create a different culture and a productive collaboration in the series of GISSI trials over the following 20 years (see Table 1).^{23,25}

Simple design and operational instruments: One of the features considered in the methodological papers referenced above was the ‘simplicity’ of the design and operational instruments used in GISSI trials. These facilitated effective participation by care-oriented health workers in population-relevant projects. ‘Simplicity’ did not mean oversimplification or approximation. It demanded selection of data and operational strategies to focus on what was essential for achieving the pre-defined aims of rigorously designed and monitored projects with patient-important outcome end points. The results of GISSI trials have been accepted not only by scientific journals but also by drug licensing agencies in the USA and Europe.

Full independence of the process of research: The GISSI trials have strictly observed full independence of the whole process of research, from the selection of the hypotheses to be tested, to the formulation of protocols in close collaboration with field investigators, to data analysis and timely publication of results. This independence was in line with the overall policy of the Mario Negri Institute for drug evaluation.¹ The first GISSI trial⁶ was conducted as an expression of a commitment to a research goal which coincided with a NHS priority. This was achieved with voluntary participation of clinician investigators, without payment or *ad hoc* grants, and with costs per patient which appear incredible today (see Table 1).

GISSI has maintained a consistent and rigorous approach, even when faced with the new scenarios

introduced with the Good Clinical Practice-International Committee on Harmonisation (GCP-ICH) rules. The support of pharmaceutical companies became necessary to comply with increasingly competitive and bureaucratically burdensome legislation and the increasing cost of trials in the trials ‘market-place’. A clear and transparent pre-defined policy of exclusive GISSI data ownership ensured that only when the trial results had been accepted for publication would the trial datasets be made available for registration purposes.

Collaborative dialogue with other independent research groups: How specific and reproducible is the GISSI experience? The broad cultural atmosphere during the 1980s and 1990s was very different from the atmosphere that has become dominant during the 21st century. The interaction and the collaborative dialogue across independent research groups in the past reflected a cultural attitude, which went beyond professional expectations or requirements. This ethos has come under constant threat in circumstances in which the market is so dominant and public investment in research so inadequate. From the creative team in Oxford, to those at NIH and later in Canada, to the collaboration with the Veterans Administration, to the Scandinavian groups, and even to the first US ‘megatrialists’: the permanent denominator of those collaborations (although not without occasional conflicts) was the focus of research on unmet public health needs, set above the almost exclusive current target of drug registration. Even some of the methodological evolutions – from the policy on transparency, to the debates on patient information,²⁶ to the justification of combined end points – provided opportunities for open discussion of differing opinions. These have been replaced by passive acceptance of rules mostly produced by the GCP-ICH world, and the seemingly endless and largely unproductive recommendations on the conflicts of interest which have dominated the scene over the past 20 years.

Implications

The global events that ushered in a new era were already visible in the mid-1990s with the creation of the World Trade Organization and in the inverse hierarchy of values proposed by the philosophy and practice of epidemiology imposed by the Global Burden of Disease.²⁷ These made the visibility and the outcome of patients less relevant than the obsessive focus on the economic burden of diseases.

There appears recently to have been signs of a ‘re-discovery’ of the need to develop or to return to an approach that recognises that actively ‘learning

health systems²⁸ are needed to assure ‘sustainability’.²⁹ Perhaps these can be seen as an indication that the scientific, methodological and cultural lessons from the era of GISSI-like experiences may yet be resuscitated.

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