

The Results of Major Clinical Trials

Critical Assessment, the Circulation of Information and Media Coverage

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Abstract

The round table elected to focus its discussion on trials that, in terms of their importance, are likely to modify medical practices and behaviour. Such trials may be pre- or postmarketing studies. For the findings of a trial to result in a change in practice, they must be credible and fulfil the basic methodological criteria. It is nonetheless appropriate to complete that binary assessment by the use of an assessment checklist appropriate to each category of users, i.e. the Regulatory Agency, prescribing physicians and patients, who are sometimes informed directly by the media. The members of the round table proposed the 'Giens 2003 checklist'. It consists of an interpretative semi-quantitative assessment checklist based on simple messages relevant to practice. Critical assessment is a necessary prelude to the circulation of the results to the various parties involved (healthcare professionals, patients, patient associations, the media and the general public) and the process of informing those parties in readily understandable but accurate terms. The practical implementation of the results, with a change in behaviour and/or the issuing of guidelines, are subsequent stages for which a certain lag time is inevitable. The assessment of implementation programmes, together with an accurate analysis of the obstacles to changing medical practice, should, in the future, improve and accelerate the implementation of important results in order to optimise patient management.

1. Introduction

Major advances in the therapeutic management of diseases are based on the demonstration of proof of efficacy and safety using a scientific approach. In the hierarchy of levels of proof, it is commonly accepted that large-scale, randomised, double-blind, controlled trials generate the most reliable evidence. Despite their reliability, and perhaps partially because of the degree of sophistication of the methodology of controlled trials, their results are frequently applied incorrectly, insufficiently or with an excessive delay after initial publication. There is frequently a long lag time between the demonstration of proof and the subsequent change in behaviour that should be of benefit to patients and the public health system.

Discoveries are only useful if they are used. It is therefore fundamental to address the optimal implementation of the results of clinical trials and promote appropriate methods of achieving that objective. The methods include improving the training of and

information for all the stakeholders involved in the practical implementation of therapeutic strategies. This article, which summarises the proceedings of a round table at the Giens 2003 seminar, focuses on defining the methods and the resources for their implementation. Critical reading of the results of major trials, using a reading checklist, is stressed. This article proposes a simplified checklist adapted to the public being addressed. The round table also tackled the question of methods of implementation, i.e. the methods for application of the results of major trials after validation of those results using the reading checklist.

2. Definition of 'Major Trials'

There are several definitions possible for the term 'major trial' and each is open to criticism:

- A trial may be large-scale without necessarily addressing a pertinent question or generating a response to the question raised.

[†] For a list of participants, please see the end of the article.

- Trials on a limited scale may nonetheless be important in terms of the question raised and the credibility of the results, and may constitute a response to a strong medical need. This is the case for certain trials on cancer agents, anti-AIDS drugs, antibiotics, etc.
- Lastly, certain large-scale trials, with irreproachable methodology, reach the result stage when the response to the issue addressed has lost its pertinence because of the results of other studies.

The round table decided to restrict the discussions to trials that, through their importance and scale, and the pertinence of the clinical results, are liable to modify medical practices and behaviour. The trials may be pre- or postmarketing studies. Studies of orphan diseases or those involving small populations constitute the subject of a specific round table and will therefore not be addressed here.

3. Result Credibility

In order to be credible, the objective of a study must reflect a pertinent question. The pertinence of the question raised is documented in detail in the publication of the rationale and design of the study after a careful review of the literature. The question addressed is based on a pathophysiological hypothesis derived from experimental studies and clinical pharmacology data.

In addition, a study can only acquire credibility if it fulfils the basic methodological rules for clinical trials. The round table proposed an initial checklist that resulted in compilation of the 'technical checklist' (table I).

The trial must be comparative, evaluating an intervention (e.g. a treatment strategy) in a group of patients versus a placebo or a comparator group, as a function of the documented data available. The comparison is conducted after randomisation of

the patients. Whenever possible, i.e. in the majority of cases, the randomised allocation is to be conducted with both the patient and physician blinded (double-blind design).

The primary endpoint of the study is to be defined and justified, prior to the study and with precision. The clinical pertinence must be clear. The patient inclusion criteria should be clearly defined. The number of enrolled patients (sample size) is to be justified statistically as a function of the risk of expected events in the control group (to be documented in the literature) and the magnitude of the expected effect.

The patient characteristics are to be provided in detail and the comparability of the various groups demonstrated.

The duration of the study must be sufficient for the expected primary endpoint events to have the time to emerge.

The statistical analysis is to be faithful to the initial hypothesis, conducted on all the patients randomised, irrespective of the duration of their participation in the study (intent-to-treat) and, possibly, completed by an analysis taking into account the duration of participation (per protocol).

Lastly, the results will only be taken into account if they are 'statistically' significant for the primary assessment criterion, i.e. the risk of a random finding should not exceed 5%.

Unless a positive response can be given to all the questions raised by the technical checklist, it is not permissible to draw a conclusion on the study under review.^[1,2]

4. What is the Significance of Meta-Analyses?

Meta-analyses consist of a review of published studies and, as a consequence, may reveal results that cannot be discerned when the studies are considered separately. Meta-analyses must not include dissimilar studies or biased studies. Meta-analyses sometimes overlook negative studies, which are frequently not published.

When it is not possible to conduct a major study, meta-analyses can be extremely useful. However, they are no substitute for a large-scale study. In a positive meta-analysis, there must be at least one study that is positive when considered separately.

5. Applicability of the Results: 'The Giens 2003 Checklist'

Once the basic credibility of the study has been established, its results must be made known to and correctly understood by the various targets involved (reviewers, prescribing physicians, journalists, patients).

The results must thus be translated into appropriate and practical terms for each of the targets. The round table compiled a second checklist that may be used by reviewers, prescribing phy-

Table I. Technical notice for a clinical trial

	Yes	No
Randomisation		
Control group		
Optimum blinding		
Relevant inclusion criteria		
Justified primary endpoint		
Sample size		
Comparability		
Legitimate study duration		
Analysis		
precise		
adapted		
ITT - PP		
p < 0.05		

ITT = intention to treat; PP = per protocol.

Table II. The Giens 2003 checklist

'PRACTICAL' items	OK (certain)	Well..., OK (probable)	Poor (dubious)	Unacceptable (no)	ND
Pertinent aim					
Representative population					
Relevant endpoint					
NNT					
Absolute risk					
Compliance					
Risk/benefit ratio					
Indication influence					
Influence on rational use					

ND = not determined; **NNT** = necessary number of treatments.

sicians, journalists and patients. It would be advisable for the checklist ('the Giens 2003 checklist') to be promoted by all the parties involved (table II).

The items addressed are practical and the assessment of the criterion is no longer binary, as it was for the technical checklist, but semi-qualitative.

The critical reading of the study using the checklist must, above all, enable a response to be formulated to the questions raised by the various targets as indicated in table III.

Let us consider the population studied in the trial as an example. The press will raise questions as to whether the population is pertinent in public health terms. The prescribing physician will ask him/herself whether, among his/her patients, there are patients resembling those in the study. The patient will only be interested in the results if the disease of the patients under study is the same as his/her own.

A further example: for the risk/benefit ratio, considered by the press in terms of impact on the population, the prescribing physician will ask him/herself if the ratio is 'reasonable' for his/her patients, while the patient will want to know if the benefit demonstrated is sufficient for him/her to take the risk of the treatment.

In conclusion, this interpretative checklist gives the study an 'artistic note' with simple messages suitable for each recipient. Completion of the checklist, for each study, requires training for both those issuing it and its recipients. It can be completed by any user or group of users concerned. Circulation and promotion of the checklist could be ensured by all the players involved, the French Agency for the Safety of Health Products (Afssaps), Leem (Les entreprises du médicament), medical representatives, the press, trainers, etc.

Afssaps could use the checklist, after having adapted it, in the review of marketing authorisation applications, in compiling Transparency Commission opinions and those of the Advertising

Commission, in compiling recommendations and in drug safety monitoring.

For marketing authorisation applications and Transparency Commission opinions, the checklist could be used as an addendum to the technical dossier and, possibly, to data validation. The checklist could also assist the Advertising Commission in evaluating the use made of the data, particularly in promotional media.

The special case of major trials not included in a marketing authorisation application but subject to an opinion from the commissions (Transparency, Advertising, recommendations, drug safety monitoring) has been raised. The 'Giens 2003 checklist' is also applicable in that case.

The recommendations and guidelines issued by official organisations (ANAES [Agence Nationale d'Accréditation et d'Evaluation en Santé], Afssaps) or academic societies are derived from evidence-based medicine.^[3] The recommendations are formulated after validation of the data (frequently after an interval of variable length, after the initial presentations/publications of the results). Drafting and issuing guidelines should be facilitated by use of the checklist compiled by the present round table.

- Prescribing physicians receive information through all the existing channels: the medical and lay press, medical representatives, pharmacists, in-service training, etc. The information validated by Afssaps reaches physicians after a time lag that cannot be shortened after the initial publication of results. During that interval, the user checklist should enable physicians to select the data sufficiently relevant to influence their practice.
- Patients frequently receive information through the press, which has few resources for assessment of the validity of results. The press frequently calls on an 'available' expert, most frequently in the context of 'urgent information'. In order to communicate pertinent information, the expert solicited should make use of the checklist.

Table III. Checklist adapted to various targets

Item/target	Press	Physician	Patient
Aim	Public expectation	I consider this a problem	I feel involved
Population	Epidemiology, public health	The same patients as mine	Same disease as mine
Endpoint	Understandable for the general public/reader	Morbidity-mortality, relevant to my practice	Affects my health
NNT	Definition	How many treatments for one patient improved	NA
Absolute risk	Definition AR > RR	Definition AR > RR	% probability of improvement
Applicability (compliance with treatment)	They will manage	He/she will manage	I will manage
Risk/benefit ratio	Risk/benefit	Is it reasonable?	Should I take the risk for that benefit?
Indication influence			
Practical influence			

AR = absolute risk; **NA** = not applicable; **NNT** = necessary number of treatments; **RR** = relative risk.

6. Circulation of Information

Except for safety alerts, where Afssaps and the experts rapidly make a statement available to the press, the latter should rarely be confronted with urgent situations. The financial press is also a special case. In the event of an immediate communication, the experts consulted could use the checklist.

After validation, the information is circulated through multiple clearly identified and frequently well informed channels. The channels were not discussed during the round table.

7. Influencing Clinical Practice

A single study rarely results in a recommendation: several convergent studies or sets of data are necessary in the majority of cases. The production and circulation of recommendations/guidelines do not guarantee their implementation by prescribing physicians.^[4]

The practical implementation of the results of clinical trials is frequently delayed, by several years sometimes, with respect to the initial publication of the results. The delay is unforeseeable and depends on numerous considerations. A number of examples drawn from the field of cardiology are considered below:

- There are studies whose results tolerate no discussion: for example, the studies of reperfusion in the acute phase of infarction. The results of two trials (GISSI [Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto miocardico]^[5] and ISIS 2 [Second International Study of Infarct Survival]^[6]) provided compelling evidence in favour of the use of reperfusion in myocardial infarction and rapidly led to a universal change in practice.
- In heart failure, the use of angiotensin converting enzyme inhibitors became widespread subsequent to several studies that provided strong and identical results, supported by a

coherent pathophysiological explanation and strong promotional support from several pharmaceutical companies.

- With regard to aspirin (acetylsalicylic acid), 100 studies carried out over 15 years were reviewed in a meta-analysis that presented a formal conclusion with respect to the prevention of infarction and cerebrovascular accidents in patients presenting with atherosclerosis. Between 1988 and 2003, in the various studies, the percentage of patients included in secondary prevention studies increased from 37% in the Scandinavian Simvastatin Survival Study (4S)^[7] to 92% in the European trial on Reduction Of cardiac events with Perindopril in stable coronary Artery disease (EUROPA)^[8]. In contrast, primary prevention in patients presenting with risk factors remains infrequent (no indication, no promotion, etc.).

Concerted action by all the players, in particular the prescribing physicians, the regulatory authorities and funding organisations is indispensable in order to induce a change in behaviour. Several monitoring methods have been tested to evaluate the impact of recommendations and/or promote their implementation.

Among those methods, the following may be cited:

- *Academic detailing*, a concept born in the 1980s and based on an advising physician visiting a prescribing physician.^[9] The advising physician is, for instance, thus able to promote an official recommendation. The programme launched by the CNAMTS (Caisse Nationale d'Assurance Maladie des Travailleurs Salariés) in June 1999 constitutes an example. The programme addresses the management of type 2 diabetes mellitus and is designed to improve control of the disease by means of a Hb (haemoglobin) A_{1c} assay and screening for degenerative diseases.^[10]

- *Audits with feed-back based on the extraction of information from the medical file and its exploitation by a third party.* The reviewed information is then given either to volunteer physicians or to all the physicians in the form of key facts.
- *Profiling methods intended to define compliant or refractory physician profiles.* This method is widely used by US managed care organizations (MCOs).^[11,12]

The effectiveness of measures involving financial incentives that may be negative, such as the recommended prescribing practices (RMO) in France,^[13] or positive, with the new French convention provisions, is under study.^[3] Among the recent examples of conventional agreements, it is worth citing the dispensing of palliative care at the patient's home by the general practitioner, the management of insulin-dependent diabetic patients aged >75 years by nurses, and the implementation of functional assessments in the context of physiotherapy.^[14]

A recent article has reviewed the efficacy of educational techniques in changing provider behaviour.^[15] The publication consists of a meta-analysis of all the randomised, controlled studies on educational methods. The conclusions are as follows:

- Academic training and training for local opinion leaders are frequently associated with a clear benefit.
- Reminder systems may be of value in certain specific situations.
- Audits and feedback are of clear utility, even though that utility is limited.
- Convention, congress, conference and printed programmes are ineffective.
- No methods currently used have demonstrated a substantial and lasting reproducible effect with regard to inducing changes in physician behaviour.
- The relative cost/effectiveness ratio of the various methods is uncertain.

In practice, before implementing any behavioural change programme, further investigation is necessary so as to identify the key obstacles and success factors. The combination of several effective techniques involving all the major stakeholders is recommended.^[16-18]

Modesty, patience and perseverance are indispensable for the success of these approaches.

8. Safety

The safety assessment must never be overlooked in the review of a study. Even though the data generated by a single study are not sufficient to enable complete evaluation of the safety profile of the drug, they nonetheless enable determination of the risk/benefit ratio of the drug used under the study conditions.

Safety data are generally covered very succinctly in the results of studies, unless safety constitutes one of the specific objectives of the study. The methodology for adverse event collection must be clearly described (management of clinical and laboratory adverse events and dissemination of information, inclusion or non-inclusion of study events in the adverse effects, management of abnormal laboratory results, severity assessment scale).

The data and safety monitoring board is responsible for compiling a monitoring plan and defining the alert limits.

It is crucial for safety information to be communicated without any pressure, be it scientific, financial or media-related. In the context of an alert, appropriate resources must be set up to inform the players (investigators, the company, Afssaps, patient associations, financial analysts and journalists) and the targets involved (healthcare professionals, patients, shareholders, the general public, company personnel, etc.) using short-term resources (press releases, Afssaps sites, 'dear investigator letter' [DIL], 'dear doctor letter' [DDL], call centres, follow-up visit by a medical representative, etc.) with appropriate reaction times, for all those involved. In the longer term, the dissemination of information will be taken up by publications, in-service medical training, medical representatives and recommendations.

9. Conclusion

The three obstacles identified with regard to changes in prescribing physician behaviour are ignorance, disbelief and inaction. With regard to the first two, the Giens 2003 checklist seems to be a relevant instrument in terms of its didactic role, which will contribute to the credibility of information and shorten validation intervals (information, acceptance). With regard to inaction, the establishment of implementation programmes is a discipline still in its infancy, as was clinical trial design and set-up in the 70s and 80s. The development of the new discipline indubitably deserves encouragement.

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