



Interim results in clinical trials: Do we need to keep all interim randomised clinical trial results confidential?



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ABSTRACT

Objectives: Guidelines for the conduct of clinical trials emphasize the importance of keeping the interim results from the main endpoints confidential, in order to maintain the integrity of the trial and to safeguard patients' interests. However, is this essential in every situation?

Materials and methods: We review the evidence for these guidelines and consider recent randomised trials that have released interim results, to assess their impact on the success of the trial. However, because the strength of opinion to keep interim results confidential is so strong, there are limited examples of such trials.

Results: In the QUARTZ trial (which is assessing the value of whole brain radiotherapy in patients with brain metastases from non-small cell lung cancer) the decision to release interim results was taken in response to threatened closure due to poor accrual, whereas in the GRIT trial (which compared two obstetric strategies for the delivery of growth retarded pre-term fetuses) the regular release of interim results was pre-planned. Nevertheless there are a number of common factors between these two trials. In particular, the trial treatments were already in wide use, with no reliable randomised evidence on which treatment should be used for which patients, and there was diverse clinical opinion, which meant that accrual was likely to be challenging. In a situation where a quarter to a third of trials do not accrue their required number of patients, the QUARTZ trial continues to accrue patients, and the GRIT trial successfully accrued its target of nearly 600 babies.

Conclusions: This article therefore argues that there is a need to re-consider whether it is always essential to keep the interim results of randomized clinical trials confidential, and suggests some criteria that may help groups planning or running challenging trials decide whether releasing interim results would be a useful strategy.

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1. Introduction

In the early days of randomised clinical trials, the common practice was to keep investigators informed about the results as they accumulated during the course of the trial. However, during the 1980s, maintaining the confidentiality of interim results gradually became accepted as a cornerstone of good clinical trial practice, ostensibly to avoid the risk of widespread pre-judgment of unreliable results based on limited data, and thus safeguard patient interests and enhance trial integrity and credibility.

However, the evidence for this seems scanty. For example, Ellenberg et al. [1] mainly base their recommendations on two studies. Firstly, a retrospective analysis of evolving outcomes in a trial of 2 anti-retroviral agents for HIV infected patients [2]. At the first Data Monitoring Committee (DMC) meeting there had been 19 progressions or deaths on the didanosine arm vs 39 on the zalcitabine arm ($p=0.009$), but as the difference had not reached the protocol-specified stopping rule, the DMC allowed the trial to continue. By the final DMC meeting this difference had disappeared (157 vs 152 events) [3]. The assumption was that if the early interim results had been made public the trial would have stopped. The second piece of evidence was a matched-analysis of the 10 most recent randomized trials run by 2 major US Cancer Cooperative Groups [4]. The analysis indicated that in the Group that released interim results to investigators, accrual declined in half of the trials, and

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one trial was inappropriately terminated early. Whereas the trials run by the Group that kept interim results confidential were considered free of problems. However, as the authors admit: ‘there are many differences between the Groups that could have contributed to this’.

Despite this apparent lack of evidence, numerous papers [5,6] reiterate this widely held view that releasing interim results destroys the integrity of a trial and operates against the interests of patients. Subsequent challenges to this new orthodoxy have been rare. Thus when an editorial [7] argued for the release of interim data in certain circumstances, and that it was unethical to withhold interim results from patients already on, or considering joining, a trial, it provoked numerous responses, citing the risk of unpredictable point estimates, pressures from interested parties, and the importance of relying on the DMC for independent decision-making.

Nevertheless, we argue that there are specific circumstances where releasing interim results will enable challenging trials to be completed successfully, and will not destroy the trial’s integrity or credibility. We describe two instances where this alternative approach has been taken.

2. Recent trials that have released interim results

The QUARTZ trial was launched in December 2006 with the aim of accruing 1000 patients to investigate the value of whole brain radiotherapy (WBRT) for patients with inoperable brain metastases from non-small cell lung cancer (NSCLC). For decades, WBRT has been advocated for such patients, but it can cause significant toxicity, and overall benefits have never been demonstrated in a randomised clinical trial. As a result different clinicians use different criteria to select which patients should, or should not, receive WBRT. However, by March 2010 only 144 patients had been recruited, and the future of the trial was in doubt.

Numerous attempts had been made to increase accrual, including presentations at national meetings, teleconferences with investigators to discuss recruitment strategies, newsletters, visits to centres, editorials in journals, and reducing the sample size to 534 patients (based on the event rate in the first 50 patients in the control group), but accrual rarely reached the required target of at least 10 patients a month.

Therefore it was proposed that the interim results should be released. The rationale behind this was the belief that a key reason for the poor accrual was the lack of any preliminary randomised data to support the trial’s hypothesis that omitting WBRT was unlikely to be detrimental in terms of either survival or quality of life. The proposal was discussed with the trial’s oversight committees and funders, neither of whom had knowledge of the interim results (as this might have biased their judgment), and approval for the release was granted following extensive discussions regarding the options and implications. The interim results were presented to investigators on 1st October 2010, with input from senior statisticians to avoid over-interpretation. The interim results (which showed no clear evidence of a difference between the trial groups), were subsequently published [8].

In the 12 months prior to the release of these interim results, accrual averaged 6.92 patients a month, and in the subsequent 12 months this increased slightly to 8.75 patients, although this may simply reflect the underlying increase in accrual seen over time and/or the added publicity about the trial, but importantly the trial was able to continue. By the end of December 2012, 398 patients had been randomized, and trial is now on course to complete accrual.

The Growth Restriction Intervention Trial (GRIT) compared two obstetric strategies for the delivery of growth retarded pre-term

fetuses: relatively early delivery (to pre-empt terminal hypoxaemia) compared with delaying delivery for as long as possible (to increase fetal maturity). Preliminary structured analyses had revealed that obstetricians were using both of these approaches, and were using different criteria to decide which approach to adopt, and thus did not have sufficient uncertainty about which individual patients would be eligible for a randomized comparison. It was decided to release the interim results to the participants at each investigator meeting in the hope that this might re-assure individual obstetricians about the approach they did not usually favour, and thus increase their willingness to approach women about the trial [9,10]. The trial design avoided frequentist statistical concerns regarding multiple interim analysis by adoption of a Bayesian updating approach [11]. GRIT successfully accrued 588 babies, and provided important evidence to inform practice [12,13] and thus the fact that interim results had been regularly released to all participants does not seem to have affected the integrity of the trial. Indeed it can be argued that a trial which releases interim results and continues to complete target accrual is likely to be far more credible than a trial which terminates early for poor accrual.

3. Criteria for the release of interim results

The experience of the QUARTZ and GRIT trials has been that the release of interim results has not compromised the success of the trial, but actually helped the trials to continue. Although these two trials are very different, they nevertheless have a number of factors in common, which might form the criteria that other groups running challenging trials might consider when assessing whether to release interim results:

- All trial treatments were already in wide use, with no reliable randomised evidence on which treatment should be used for which patients.
- There was diverse and strongly held clinical opinion, which meant that accrual was likely to be challenging.
- The trials employed short-term interventions, meaning that disclosure of the interim results would not impact on the treatment of current patients, and trial comparisons.
- A sufficient number of reliable outcomes were available in order to make comparisons.

Thus we believe that, when all other attempts to revive declining accrual has failed, trial groups should consider the possibility of releasing interim results, although the operating characteristics of each trial need to be considered carefully from both scientific and ethical perspectives.

Any consideration of releasing interim results will be a judgment call, and must weigh up the risks that releasing interim results may be over-interpreted, may negatively affect accrual, and/or may affect subsequent secondary treatment (and thus bias long-term results), against the risk of the trial failing to accrue sufficient patients to produce a reliable result. The interim results from the two trials described above were non-significant and of course raise the issue of whether an interim, potentially false-positive, result would have caused the trials to stop inappropriately prematurely. Unfortunately given the lack of trials where interim results have been released we can only speculate how participants might react to seeing a significant result, but, as indicated above, it is vital that the implications of releasing interim results are carefully explained by experienced statisticians.

4. Conclusions

It is always important to revisit and reflect on current practice. We increasingly live in a climate of freedom of information, transparency and openness, the research and clinical communities are now more knowledgeable about trials, the profile of clinical trials is higher, the Internet allows everyone greater access to information, and the concepts of uncertainty and risk are more widely discussed. Evidence-based medicine depends on sufficiently large amounts of evidence from randomized trials. Therefore any trial group that fails to predict poor accrual and/or stops the trial prematurely due to failure to accrue (it has been estimated that between a quarter and a third of trials do not achieve their planned accrual [14,15]) fails to advance knowledge and squanders resources as well as the goodwill of participating patients, which represents an unacceptable waste of research funding, investigators time, and patients goodwill. In these circumstances, we believe there is a need to reconsider and debate the current attitudes towards the release of interim data.

Authors' contributions

RS wrote the initial draft and incorporated comments from all of the other authors. All authors have approved the final version.

Conflict of interest statement

The authors declare that they have no competing interests.

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