Journal of Clinical Periodontology
Official Journal of The European Federation of Periodontology
Founded by the British, Dutch, French, German, Scandinavian, and Swiss Societies of Periodontology

J Clin Periodontol 2008; 35: 681–682 doi: 10.1111/j.1600-051X.2008.01252.x

Journal of Clinical Periodontology

Letter to the Editor

ITT in respect to GCP: a matter of diligence

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Van der Weijden F, Slot DE, Rosema M, Timmerman M. ITT in respect to GCP: a matter of diligence. J Clin Periodontol 2008; 35: 681–682. doi: 10.1111/j.1600-051X.2008.01252.x.

Accepted for publication 27 April 2008

Dear Editor,

Good Clinical Practice (GCP) is an international quality standard that is provided by International Conference on Harmonisation (ICH). This is an international body that defines standards on how clinical trials should be conducted, which governments can transpose into regulations for clinical trials involving human subjects. These guidelines include protection of human rights as a subject in clinical trials. It also provides assurance of the safety and efficacy of the newly developed compounds.

One of the basic aims of GCP is to protect the subjects involved in research. According to the guidelines a subject is not obliged to give his/her reason(s) for withdrawing prematurely from a trial (§ 4.3.4, ICH Topic E 6 (R1), Guideline for Good Clinical Practice). The investigator should make a reasonable effort to ascertain the reason(s) for withdrawal, while fully respecting the subject's rights. These rights are also formulated in the Declaration of Helsinki (paragraph 22): ''*... Subjects have the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal ...*'', and in the Dutch Law (WMO paragraph 1, section 4). Optimal care for subjects implies: ''*... That an investigator should act primarily to ensure the well-being of the subject and only then pay attention to the administrative obligations. This is often forgotten in the entire complex clinical research process ...*'' (Pieterse 2000).

It is a common phenomenon, that a number of patients do not complete a study. For different reasons, they drop out from active treatment and thus are not assessed at the end of the study. At this stage, application of the GCP ethical principles may introduce a methodological and/or statistical problem. Consequently, there appears to be a conflict between these principles and the intention-to-treat (ITT) principle with respect to how drop-outs are being handled during the study. This is the point we want to raise.

ITT covers three distinct issues: drop-outs, adherence and missing data (Dallal 2007). According to the glossary of terms of the CONSORT guidelines ITT analysis is a strategy for analyzing data in which all participants are included in the group to which they were assigned, regardless of whether they completed the intervention given to the group. ITT analysis prevents bias caused by loss of participants, which may disrupt the baseline equivalence established by random assignment and may reflect non-adherence to the protocol (Altmann et al. 2001). According to the ITT principles one would do everything possible to reduce the number of dropouts (Ellenberg 1996, Dallal 2007) and may even go as far as imputing missing data. Many imputation methods have been suggested, but there is nothing that can be done without making critical unverifiable assumptions: assumptions that are critical for the outcome of the study, but cannot be verified for their appropriateness. All of the approaches are merely different ways of forecasting what the final measurement might have been (Dallal 2007). Using these imputation methods implicitly influence the data set of a study, but to what extent the outcome is of a higher value and closer to the truth remains unclear.

A statement frequently heard in relation to ITT is ''once randomized always analyzed'' which is a reflection of the following: ''*... The principle of attributing all patients to the group to which they were randomized results in an intention-to-treat-analysis, which is analysis of outcomes based on treatment arm to which patients were randomized, rather than which treatment they actually received. This strategy preserves the value of randomization ...*'' (Guyat & Rennie 2002). The randomization procedure may be at risk with an as-treated analysis and may provide a misleading estimate of the true treatment effect.

However the research question may direct the analysis into another direction especially at the early development stages of a product. Protocol adherence violations may occur where participants do not receive the full intervention. In a study where the main interest is the ''proof of principle'' the analysis could focus in first instance on those participants who fulfilled the terms of the protocol (per protocol analysis-PPA) (Altmann et al. 2001). The major difference is that ITT will include ''noise'' in the data while the PPA tries to exclude it. The PPA may result in an overestimation of what the effect may be in ''real life''. However this will not be a problem where the ''proof of principle'' of efficacy is concerned and adherence issues are not part of the research question. The purpose of a study (the research question) is therefore an important issue of distinction in this discussion. Also when there are different definitions of the endpoint such as ''equivalence'' or ''efficacy'' (Ellenberg 1996). An ITT analysis may be appropriate in some cases, but it is not a magic charm (Dallal 2007).

There are two components to how a treatment will behave in a population at

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large: *efficacy and adherence*. These are separate issues that cannot always be addressed routinely by one type of analysis (Dallal 2007). The efficacy of a treatment is often the basic research question regardless of adherence issues. There may be cases where an ITT analysis will truly reflect the way the treatments will behave in practice because adherence during the trial will reflect adherence after the treatment is proven effective. But adherence during a trial might be quite different from adherence once a treatment has been proven effective. Also novelty-effects and Hawthorne effects may positively influence adherence. In such cases, analyses that are influenced by adherence in the manner of ITT may not even truly reflect what will happen in real life.

A suggestion for solving the discrepancy between the ease with which GCP accepts drop-outs and the rigidness with which ITT tries to keep them in is proposed by Dallal (2007). To eliminate the conflict that may be between GCP and ITT, authors should describe in detail the number and reason for drop-outs, adherence to the protocol and missing values. This in fact is the only way to solve the divergence, because human and therefore patients rights (Universal Declaration of Human Rights, article 3) overrule the importance of a ''complete'' study data set. This hierarchic way of decision-making subsequently implies that an incomplete data set is most likely the consequence.

Weighing the influence of dropouts, adherence and missing data is a diligent matter that is crucial to the validity of the conclusions drawn in a study. For the reader the assessment of the quality of a study report is very much dependent on the critical appraisal of these matters and the validity of the choices made (Guyat & Rennie 2002).

One of the dangers that lies ahead is that a solid and veritable research protocol, may be surpassed as such while conducting the study. Also for the clinical study itself ''real life'' may turn out to be different than could be reasonably expected beforehand. Ultimately the choice could be to reject the ''study outcome'' or carefully assessing as to which level a valid contribution to the dental literature can be justified. These delicate interpretations put a burden on the responsibilities of both authors and reviewers. ITT is not the easy way out for the process of well-considered, scientifically valid decision making with regard to these matters. Statistical approaches can provide a guideline for a professional judgement but should not supply the decision itself.

It seems the best approach to perform the proper analysis, which appears most appropriate to address the ''research question''. However, irrespective of the type of analysis chosen, authors should realize that according to the GCP guidelines, the protocol should state in advance the statistical methodology that will be used for data analyses. The handling of dropouts, adherence and missing data should be openly and meticulously described. Editors and reviewers should both be critical on the description of these items and unprejudiced to the choice of the analysis in the context of the obligations as put down by GCP.

In the spirit of GCP, valuable material involving the participation of human subjects should never be lost due to a rigid ''statistical and methodological'' judgement of a ''clinical'' study.

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