

THE CROSSOVER CR QUARTERLY

April 26, 2011

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EDITORIAL

FAIR MARKET VALUE?

Commercial sponsors sometimes contend during grant negotiations that their grant offer is at "fair market value". Fair market value is "the price that an interested but not desperate buyer would be willing to pay and an interested but not desperate seller would be willing to accept on the open market assuming a reasonable period of time for an agreement to arise".

Considering that an investigator and his/her institution is "an interested but not desperate seller" is far from the truth.

In many countries, there is no public support for noncommercial Clinical research (CR), and therefore, hospital physicians interested in trials for their patients, really do not have an alternative to protocol proposals from commercial sponsors. Not seldom, commercial sponsors, but more often Contract Research organizations (CROs), make investigators believe that the window for their acceptance of the grant is very narrow: "we have approached more sites than we really need" (understand: other investigators in other countries stand in line), "other sites have already approved the grant" (understand: take it or leave it), "the grant is not negotiable, because we can get the patients cheaper in emergent countries". These pressures are the fact of individual negotiators, and should not be regarded as common strategies of their employers.

Fair market value is also supposed to mean that not all activities in the patient flowchart have to be paid for by the sponsor, in particular regarding the Standard of Care (SOC). It is only right that the participant's health insurance pays for activities falling under the SOC. It is fair that the healthcare institution and the investigator are not paid twice for the same tasks. However, it is unfair that certain commercial sponsors make believe that they have a right to data collected under the SOC for free, and that investigators must evaluate and enter this data in the CRF at their own cost.

Fairness means also that real activities are compensated for. In my experience, a careful analysis of the protocol shows frequently that the flowchart contains omissions, like missing columns for "visits", missing lines for "tasks", or the omission of an occasional cross in a cell.

A systematic omission concerns the work needed to detect a candidate participant, retrieve his/her chart, carry out some in-/exclusion feasibilities all over the chart, and only then invite this person and propose the study, plus the time to document all this.

Only from 2010 did the majority of commercial sponsors and CROs at a very large hospital campus in Brussels, Belgium, admit that hospitals and investigators have startup costs from the moment the protocol is proposed to them. They will only acknowledge the startup cost if and after the Clinical Trial Agreement (CTA) is signed. A minority of sponsors still says that they only pay for the data they receive. The Investigators' Meeting is held before CTA signature, and cynics will wait to sign the CTA until the initiation visit, to avoid compensating any hospital staff time during study setup before first-patient-in.

Whereas CROs have managed to get paid per Adverse Event, per Query, and even per E-mail, we have not heard yet that hospitals and investigators will get fair remuneration for these and many other direct study-related activities.

There are also indirect costs to hospitals and investigators.

On the European Continent, institutional Indirect Cost Rates (ICRs) have only been practiced by hospitals since 2005. Still today, some sponsors say this is not part of fair market value. Some pharmaceutical physicians say their employers "are not a charity". American Academic Medical Centers have practiced ICR for at least 15 years. In the USA, the median ICR is probably 25%. Hospitals in the USA publish their ICRs on their websites. On the continent too, 25% is getting fair acceptance, although recently, the local medical representative in Belgium of a very large US-based sponsor stated that his company pays a maximum ICR of 20% because anything above is unfair. In the Clinicaltrials.gov database, this sponsor appears to place 23% of its clinical trials in the USA...

Occasional negotiators use the notion of Fair Market Value to serve multiple unfair purposes.

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STANDARD OPERATING PROCEDURES REVIEWING A CLINICAL TRIAL PROTOCOL

All investigators, members of Ethics Committees and Institutional Review Boards, and many other scientists in regulatory bodies, at CROs and Clinical Research Units in hospitals, need to review proposed protocols, whether commercial or non-commercial. This review is crucial before decision-making, such as: Do we invest in this trial?, or Do I take on this trial as an investigator?, or Do we spend time budgeting this trial?

Usually, each reviewer has a personal approach to reviewing a proposed protocol. Sometimes, reviewing a protocol is a moving target, where the proposed protocol is an early draft, or just a synopsis, and one anticipates that several versions will follow. Since the review is often not systematized, and reviewers do not always realize clearly how to organize the review, reviewers rarely share their opinions in more detail than vague subjective judgments, such as: good or bad; I like it or I do not like it. This does not help colleagues also reviewing the same protocol, and there is little or no useful feedback to the protocol writer(s). Protocols are complex documents, especially in the pharmaceutical industry. They can be very bulky documents, written in highly specialized language. On the contrary, non-commercial protocols (so-called academic protocols) are often hopelessly simple with

important sections missing, such as the definition of the primary endpoint, the statistical hypotheses, the sample size calculation and/or the statistical test which will be used to analyze the results concerning the primary endpoint.

How to write a protocol is not really taught, except to clinical pharmacologists and pharmaceutical physicians. ICH has published in 1996 Good Clinical Practice Guidelines (ICH-GCP). In chapter 6, guidelines are provided how to write a clinical trial protocol, but they are not very detailed.

Crossover has designed a standard protocol review form, reproduced below, which we use to review new proposed protocols. For each section which should be available in a protocol, the form provides hints at the minimum content required. Each reviewer can add remarks, and then decide in the right hand column whether to accept or reject each section of the protocol. An overall appreciation can be provided at the end. The order of the sections can vary from protocol writer to protocol writer.

It is not the number of pages which makes a good protocol, but the extent to which all important issues have been dealt with. This form can be used as a checklist. ■

Crossover Template

CONFIDENTIAL

Page X of Y

SCIENTIFIC REVIEW OF PROPOSED PROTOCOL (SROPP)

Title			
SPONSOR AND STUDY		SITE/COUNTRY	REVIEWER
Sponsor:	Study Acronym:	Hospital:	Affiliation:
CRO:	Nr:	PI:	Name:
IMP:	Version:	Dept:	Title:
Indication:	Protocol Date:	Coord Inv.:	Review Date:
Protocol section	General recommendations and specific remarks		Accept
1. Title	Should contain design, drugs and dosage, indication, objective, target population. Remark:		Y/N
2. Title page	Should contain title, "Confidential", protocol number(s) (IND, EUDRACT where applicable), clinical phase, date, version, status, sponsor and contact details. Several pages may be required if more stakeholders are listed (e.g., central lab, monitoring organization, statistician, expert panel(s)). Optional: short title and/or acronym, confidentiality statement, author and contact details. Remark:		Y/N
3. Header/footer	Sponsor name and/or logo, short title, "CONFIDENTIAL", pagination, date, version. Remark:		Y/N
4. Signature page	Text before signature needs to certify compliance with the protocol, SOPs, ICH-GCP, all applicable regulations and Declaration of Helsinki. Remark:		Y/N
5. Table of content	Remark:		Y/N
6. List of abbreviations	Remark:		Y/N

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7. Synopsis	See structure of synopsis prescribed by ICH (www.ICH.org ; <guidelines> - efficacy – E3 Structure and content of clinical study reports: http://www.ich.org/LOB/media/MEDIA479.pdf - Annex I) Remark:	Y/N
8. Introduction with rationale	Description of the scientific basis for this protocol, why there is a need to do this study, what is the underlying medical hypothesis, who might benefit, why these products & dosages are used. Remark:	Y/N
9. Objectives	Objectives should be worded with great care; they should be ranked: primary, secondary and exploratory; each objective should relate to appropriate parameters defined in the protocol, and these in turn should be assessed statistically with appropriate methods. The sample size must be adequate for the primary objective at least. Remark:	Y/N
10. Study design	A study diagram must be provided. Remark:	Y/N
11. Study population	In-, and exclusion criteria at screening and during the study. Remark:	Y/N
12. Parameters	To be linked with the various objectives (e.g., efficacy and safety). If special equipment is needed, it is described. If special procedures must be followed, they need to be described, perhaps in an Annex. Remark:	Y/N
13. Schedule of assessments	Flowchart (obligatory); for each visit a summary of assessments to be made (optional). Remark:	Y/N
14. Study medications	(Dis)allowed concomitant medications; description of investigational products (active substance, composition of final products, packaging, labeling, method of distribution, source, manufacturer, method of decoding if blinded), method of allocation of patients to the treatments (e.g., randomization). Remark:	Y/N
15. Safety	Classification of adverse events, classification of relatedness with investigational products; communication of (serious) adverse events; stopping rules; safety management board if any. Remark:	Y/N
16. DM & Stats	Description of the statistical hypotheses (null and alternative); sample size calculation; data management procedures; need for central reviewers for one or more endpoints; statistical tests and mode of presentation of results for different parameters. Organization which will write the statistical analysis plan, do the data entry, carry out the tests, prepare the statistical report. Remark:	Y/N
17. Miscellaneous	Applicable regulations; relations with ethics committee(s); informed consent procedure; publication rights; intellectual property rights; Case Report Forms; method of monitoring; quality assurance and audits/inspections; archiving essential documents. Remark:	Y/N
18. References	Standardize the presentation of references (e.g., One author et al. or three authors et al. or all authors; Journal Name Year; Volume:1 st page-last page). Remark:	Y/N
19. Annexes	Add product information (usually the SmPC of marketed products or a product profile of research products). Remark:	Y/N

Signed by reviewer: _____

Name, Title:

(one original signed and stored).

Abbreviations: Coord Inv.= Coordinating Investigator; CRU= Clinical Research Unit; Dept.= Department; DM= data management; ID= identity; IMP= Investigational Medicinal Product; Nr.= number; PI= Principal Investigator; SmPC= Summary of Product Characteristics; stats= statistics; V.= version.

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ECONOMICS OF CR AT THE HOSPITAL

IS "MORE" TRIALS "BETTER"?

Hospitals wishing to attract CR, know their chances increase if they can show some nucleus of centralized Clinical Research Units (CRUs). This adds further losses to an already loss-making portfolio of trials. Should they become a Mayo Clinic with a portfolio of 8,000 clinical trials?

Model A. AMC model in the USA

Assuming a Research Nurse (RN) and a Clinical Study Coordinator (CSC), who cost their healthcare institution EUR60,000/year each, work together 50/50 on 10 protocols that are recruiting 10 patients each in the same year for an average grant of EUR5,000/completer, the revenue for the institution is EUR500,000 in one year. The cost of the RN+CSC is 24% of the revenue they help generate. Each study participant represents an average of 10 visits (@ EUR500/visit), which means the RN and the CSC process 1,000 visits/year. That is probably the limit for a portfolio spanning all phases. It may be too much where there are only complex studies.

Ten protocols is the number of studies a single department handles in a year at Academic Medical Centers (AMCs) in the USA, but in Europe, hospital departments have ON AVERAGE, very few studies: one study per year or less. This statistic would be worth a study supported by the European Union.

Let's assume in this model, that investigators are allowed to earn up to 40% of total revenues, after deduction of the RN+CSC, of the contribution of other departments involved and the hospital Indirect Cost Rate. Thus, EUR200,000 is earned by the investigators (maximum 10) in this model at the end of the year.

Model B. Average hospital in Western Europe

Consider a hospital where participant recruitment is low, e.g., 2.5 patients per trial on average, where 10 were expected. This is, e.g., because a third of all studies enroll zero patients, another third underperform badly, and only one third of studies enroll satisfactorily, with very few studies enrolling according to plan. The same RN+CSC with the same study portfolio will produce only 250 visits in a year. This is unbearable financially, because the revenue falls to EUR125,000, and the two staff alone will consume

96% of the revenue.

Reasonable investigators react well before such a catastrophe, typically by increasing the number of trials. They will need 4 times more clinical trials, i.e. 40 trials per year, to ensure the same income as in Model A.

Now, assume that at this fictitious hospital, departments active in CR attract no more than 2 protocols in a year, on average. The workload for the RN+CSC now becomes unbearable, because they have to span 40 trials to be conducted at 20 departments, instead of 10 protocols at 1 department. The size of the portfolio of trials for the same output in visits and the spread over many departments inside the hospital leads to a great loss of productivity for the RN+CSC. The hospital now hires 2 additional RNs and 2 CSCs, plus a manager. The new structure costs (6 x 60,000) + 110,000 = EUR470,000, the hospital must waive its ICR compensation and can only distribute EUR30,000 to investigators at the end of the year..

As Model B requires more staff, there is a greater turnover of staff, which is unsettling for investigators. Producing few case reports, each investigator earns little and considers that the game is not worth the candle. Average enrollment per trial does not improve, year after year. Good principles of governance and accounting of CR, if they are introduced at all, aggravate the losses.

Let's not forget the cost of negotiations

In a slow enrollment region, the cost of negotiations to acquire a much larger portfolio is obviously much greater. Assume trial negotiations "eat" EUR5,000/protocol at marginal cost, Model B has negotiation costs of EUR200,000/year (40% of revenues), vs. EUR50,000 (10% of revenues, which is acceptable) in Model A. It is therefore understandable that the majority of clinical sites in Europe do not read the proposed budget or contract in detail.

Model B leads to further losses and frustration. The lesson from Model B is that a reasonable financial equilibrium in CR can only come from external subsidies (unavailable in most countries and at most hospitals) or, more realistically, from a careful selection of fewer protocols which are feasible, combined with the support of a professional CRU. ■

Abbreviations: AMC= Academic Medical Center; CR= clinical research; CH= Switzerland (Confédération Helvétique); CR= Clinical Research; CRI= Clinical Research Infrastructures; CRO= Contract Research Organization; CRU= Clinical Research Unit; CSC= Clinical Study Coordinator; CTA= Clinical Trial Agreement; EU= European Union; ICR= Indirect Cost Rate; RN= Research Nurse; SOC= Standard of Care.

Crossover CRI AG (CRI= Clinical Research Infrastructures) is a company incorporated in Switzerland, which provides comprehensive nonclinical research support inside hospitals, from contract negotiations to study coordination, but also market research, and even invoicing. Crossover operates entire Clinical

Research Units (nonclinical staff, facilities and equipment) at hospitals on their behalf.

The Quarterly welcomes manuscripts concerning nonclinical issues in hospital-based clinical research.