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Memorandum

To: Center faculty, staff, and friends

Fr: Curt Meinert

Re: The type and place of publications from trials

This is the fourth memo in a series of memos concerning issues in the presentation and publication of results from trials. Previous memos have dealt with the obligation to publish, investigator right of primacy, and limits to that right.

A primary publication in the context of trials is:
A publication from a study or investigation considered essential in relation to the primary purpose or objective of a specific research project; in the case of trials, includes publications of primary results and on the design, methods, and baseline results of the trial. (Meinert; Clinical Trials Dictionary)

The obvious place for all such publication is in the world's peer-reviewed, indexed medical journals. Indeed, one can argue that publication via other routes (eg, in book chapters, "technical proceedings", stand-alone monographs, or via the "web") is not consistent with the duty to publish, as discussed in an earlier memo. It is hard to argue that the research done yields *fruitful results for the good of society* (2nd item in the Nüremberg Code) if the results are published in such obscure places so as to render them "lost" for all intents and purposes.

Investigators cannot, of course, guarantee publication of results in the medical journal of their choice because editors may reject their offerings. However, if not in the journal of their choice, then in the journal of their second choice, and so on until they succeed.

Broadly, treatment results from trials can be characterized as interim or final (from Meinert; Clinical Trials Dictionary):

interim treatment result *n* - [**trials**] 1. A **result** indicative of a **treatment effect**, as seen or produced during a trial. 2. Such a result leading investigators to stop the trial or to modify the **treatment protocol**; such a result causing the **treatment effects monitoring committee** to recommend that investigators stop the trial or modify the **treatment protocol**. rt: **final treatment result** ***Usage note***: Subject to confusion with **final treatment result**. Technically, an interim result that causes investigators to stop the trial is also a final result, but normally use of the latter term is reserved as indicated in the usage note for that term.

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final treatment result *n* - [**trials**] 1. The **result** of **treatment** as seen at the end of treatment. 2. The **treatment difference** (defn ?) observed at **close of trial** (defn 1). rt: **interim treatment result** ***Usage note***: Best reserved for use in the sense of defn 2; see usage note for interim treatment result.

The number of treatment results papers produced in a trial depends upon what happens in the trial. For example, in the case of the CDP there were three publications containing interim results and one containing final results:

Coronary Drug Project Research Group: The Coronary Drug Project: Initial findings leading to modifications of its research protocol. JAMA 214:1303 - 1313, **1970**.

Coronary Drug Project Research Group: The Coronary Drug Project: Findings leading to further modifications of its protocol with respect to dextrothyroxine. JAMA 220:996 - 1008, **1972**.

Coronary Drug Project Research Group: The Coronary Drug Project: Findings leading to discontinuation of the 2.5-mg/day estrogen group. JAMA 226:652 - 657, **1973b**.

Coronary Drug Project Research Group: The Coronary Drug Project: Clofibrate and niacin in coronary heart disease. JAMA 231:360 - 381, **1975**.

The UGDP produced two interim results papers (for tolbutamide and for phenformin) and one final results paper (for the two insulin treatment groups):

University Group Diabetes Program Research Group: A study of the effects of hypoglycemic agents on vascular complications in patients with adult-onset diabetes: II. Mortality results. Diabetes 19 (suppl 2):785 - 830, **1970b**.

University Group Diabetes Program Research Group: A study of the effects of hypoglycemic agents on vascular complications in patients with adult-onset diabetes: V. Evaluation of phenformin therapy. Diabetes 24 (suppl 1):65 - 184, **1975**.

University Group Diabetes Program Research Group: A study of the effects of hypoglycemic agents on vascular complications in patients with adult-onset diabetes: VIII Evaluation of insulin therapy: Final report. Diabetes 31 (suppl 5):1 - 81, **1982**.

In regard to primary results, publications are generally either "final" or "interim". Usually, if there is an interim publication, there will be no "final" publication for that aspect of the trial, but there are exceptions. For example, SOCA produced both an interim and final publication for the HPCRT trial:

Studies of Ocular Complications of AIDS Research Group in collaboration with the AIDS Clinical Trials Group: Parenteral cidofovir for cytomegalovirus retinitis in patients with AIDS: The HPMPC Peripheral Cytomegalovirus Retinitis Trial: A randomized, controlled trial: Ann Int Med 126: 264-274, 1997

Studies of Ocular Complications of AIDS Research Group (SOCA) in collaboration with the AIDS Clinical Trials Group: Long-term follow-up of patients with AIDS treated with parenteral cidofovir for cytomegalovirus retinitis: The HPMPC Peripheral Cytomegalovirus Retinitis Trial: AIDS 11: 1,571-1,581, 2000

Broadly, one can classify papers from trials by content as follows:

Treatment results
- **Primary** (papers containing treatment comparisons based on the primary outcome measure)
  - **Final** (papers produced at the end of the trial and based on finished datasets)
  - **Interim** (papers produced during the course of the trial as a result of data-based protocol changes; primarily the result of implementation of recommendations of changes issuing from TEMCs)
- **Secondary** (papers containing treatment comparisons based on secondary outcome measures)
- **Tertiary** (papers containing treatment comparisons based on tertiary outcome measures)

Design and methods (papers devoted to description of design and methods)

Baseline (papers devoted to description of the study population on enrollment)

Natural history (usually in clinical trials, papers describing the course of disease in the control-assigned or control-treated group)

Performance (papers devoted to description of performance or operating characteristics of the trial)

Ancillary (publications devoted to results form ancillary studies)
Other (risk-factor assessments, predictors of compliance, meta-analyses, etc)

Clearly, the process of "paper writing" is more extensive than that related merely to publication of primary results. It is common for long-term trials to generate a number of publications. The publication "record" of completed trials coordinated by people in the Center is as summarized below.

	Enrollment		Followup	# publications			Year published		
	Start	End	End	Total	Results[#]	Other[‡]	1st	Last	1st res[†]
UGDP	1961	1970	1975	8	4	4	1970	1982	1970
CDP	1966	1969	1975	53	7	46	1967	1988	1974
CDPA	1972	1974	1975	2	1	1	1976	1978	1976
HPT		1982	1983	1986	14	1	13	1987	1991
1990									
GLT	1984	1987	1989	11	5	6	1987	1995	1995
SOCA[*]									
FGCRT	1990	1991	1991	13	7	6	1992	2000	1992
CRRT	1992	1995	1995	1	1	0	1996	1996	1996
HPCRT	1994	1996	1996	2	2	0	1997	2000	1997
MACRT	1995	1996	1997	1	1	0	1997	1997	1997
GCCRT	1997	2000	2000	0	0	0	-	-	-
CAMP	1993	1995	1999	12	2	10	1994	2000	2000
Totals				**117**	**31**	**86**			

[*] Counts for SOCA trials does not include papers involving combined datasets of two or more trials; 3 papers
[#] Primary, secondary, or tertiary results
[‡] Baseline results, design and methods papers, natural history papers, and others
[†] Year of first primary results publication

Investigators have to plan the approach they take in describing the design and methods of the trial. They have to decide whether they will write a stand-alone design and methods paper. There are advantages to that approach, especially if investigators plan on producing a number of papers on results. Being able to reference a paper on design and methods is convenient when writing the methods sections of results papers.

Investigators must also decide whether they will produce a baseline results paper. The decision taken will depend on the "energy" level of the group and on the presumed value of such descriptions. The reality is that writing such papers is about as interesting as "watching paint dry", but the information can be useful in understanding subsequent papers and can be of great value to others in planning subsequent studies and trials.

They must also decide when planning to write both types of papers whether to write two papers or one. In theory, a stand-alone design and methods paper can be written any time after the trial has started, whereas a baseline paper cannot be written until enrollment has been

completed. Hence, coupling the two types of papers has the potential of slowing production of a composite design, methods, and baseline results papers. However, it is probably not wise to write a design and methods papers until well into the trial because methods are subject to change, especially early in the course of trials. Hence, coupling may not have a serious impact on production.

Among the 11 completed trials listed in the table above, only 6 produced design and methods, baseline, or design, methods, and baseline papers (table below).

	Yr of pub			1st results	Time differential
	D & M only	Bl only	D, M & Bl	publication	in mos*
UGDP			Nov 1970	Nov 1970	0
CDP			Apr 1973	Nov 1970	+29
HPT			Sep 1989	Jan 1990	-4
GLT	Aug 1991			Aug 1989	+23
FGCRT	Jan 1992			Feb 1992	-1
CAMP	Feb 1999			Oct 2000	-20

* Time differential in months: Elapsed months from publication of design and methods or design, methods, and baseline results paper and publication of the 1st results paper.

Investigators have to decide whether to use the monograph approach to publication, ie, two or more papers from the trial published back-to-back in a regular or special issue of a journal. The monograph form of publication was used in the UGDP, CDP, and HPT. In the case of the UGDP, that form was used for the first two publications – one detailing the design, methods, and baseline results and the other detailing results for the tolbutamide-placebo treatment comparison. The monograph form of publication in the CDP and HPT was used to combine a series of papers relating to design, methods, and baseline results.

The monograph approach is reasonable only in so far as journals are willing to publish papers back-to-back in a regular or special issue. Generally, that option exists only for speciality journals.

The back-to-back or monograph approach to publication has a certain appeal in that it serves to package papers in a reader friendly way. The approach, if pursued, should be pursued in concert with the editor of the target journal and then only if there is a realistic appreciation of the effort involved. It is an order of magnitude more difficult to produce a package of papers

than it is to produce papers one at a time. Packaging, when it comes to paper writing, means that production of the finished product is "controlled" by the slowest, most lethargic, writers.