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SOMETHING FOR EVERYONE: STANDARD OPERATING PROCEDURE PRODUCTS FOR THE INVESTIGATIVE SITE

By Norman M. Goldfarb

The implementation of Good Clinical Practice (GCP) varies considerably from investigative site to site, and often within sites. Standard Operating Procedures (SOPs) help study personnel conduct clinical research studies with consistent high quality. (Of course, they have to reflect the site's practices and actually be used.) They also help sites navigate the many complicated legal and regulatory requirements, and support practices that sponsors may dispute.

It is not practical, or desirable, for SOPs to spell out every last detail for every conceivable scenario. Aside from the multitude of scenarios, FDA inspectors can issue a *Form 483 – Inspectional Observations* for deviations from SOPs. SOPs should therefore have enough detail for guidance, but not so much as to be cumbersome. Sites can write SOPs from scratch, or adapt them from the seven commercial products (Table 1) reviewed in this paper. A good alternative to writing overly-detailed SOPs is to create a handbook of supporting step-by-step instructions, forms and checklists. Because the handbook is not officially part of the SOPs, updating it does not require a formal SOP review and approval process, and it is not subject to FDA inspection.

This paper analyzes the commercial products for investigative site SOPs. Each has its own unique profile of strengths and weaknesses, so none of them is best for every site. In fact, there are enough complementary strengths to recommend them all to the site with a "flexible" budget. None of the commercial products is likely to be ready for implementation right out of the box; all require review and customization for each site's requirements. Their collective scope is broader than the scope of any single product, and also broader than the scope that many sites may want to implement. Adapting and implementing SOPs is a major effort, so starting with a solid foundation is sensible.

This paper does not attempt to measure the quality of the SOPs in terms of their regulatory compliance, accuracy, and completeness. The author spotted very few erroneous statements, and not enough to conclude that any product is superior or inferior to the others in this respect. There are, however, numerous omissions, which may or may not be important. Examples include not specifying that the site should give the subject a *signed* copy of their informed consent form, or that the person who signs a document must date his or her own signature.

This paper will provide guidance for readers who are selecting a commercial SOP product for purchase, as well as help readers develop homegrown SOPs. However, no purchase decision should be made without reviewing an SOP's table of contents and at least one sample SOP. This paper may also guide the commercial SOP authors in developing their next editions.

The SOP products are reviewed in order of descending price.

Table 1: Commercial SOP Products

Title Author Publisher Format	Copyright ISBN Price (US$) Abbreviation[1]	Website Telephone Fax Email
Standard Operating Procedures for Sites and Clinical Research Team Members Paula Jones-Wright ClinCoach Inc. Binder & CD-ROM (MS Word)	2004 n.a. $1200.00 ($1700.00 Canadian) Coach	www.clincoach.com 902.463.9846 902.464.3966 pjwright@clincoach.com
Standard Operating Procedures for Good Clinical Practice at the Investigative Site Arna Shefrin and Carol Saunders Thomson Center for Clinical Research Practice, Inc. Binder & CD-ROM (MS Word)	2003 0-9663593-1-3 $995.00 CCRP	www.ccrp.com 781.431.6466 781.237-.330 info@ccrp.com
Good Clinical Practices SOP Template Manual n.a. Walter B. Morley Foundation Binder & CD-ROM (MS Word)	2002 n.a. $625.00 Morley	www.morleyfoundation.org 404.625.0036 404.745.8400 jgreen@morleyfoundation.org
Standard Operating Procedure Templates for the Clinical Site, Version 3.0 Lorraine D. Ellis and Karen S. Sargent Research Dynamics Consulting Group, Ltd. Binder & CD-ROM (MS Word)	2004 n.a. $495.00 ResDyn	www.resdyncg.com 585.381.1350 585.381.4032 info@resdyncg.com
Site Standard Operating Procedures n.a. MedTrials, Inc. Softcover Book & CD-ROM (MS Word)	2004 n.a. $350.00 MedTrials	www.medtrials.com 214.630.0288 214.630.0289 products@medtrials.com
Handbook of SOPs for Good Clinical Practice, Second Edition Celine M. Clive, Polaris Clinical Research Consultants, Inc. CRC Press LLC Hardcover Book & CD-ROM (MS Word)	2004 0-8493-2181-6 $229.95 Clive	www.polarisconsultants.com 919.463.0003 919.463.0004 cmclive@aol.com
Good Clinical Practice: Standard Operating Procedures for Clinical Researchers Josef Kolman, Paul Meng, and Graeme Scott, editors John Wiley & Sons Softcover Book (no CD-ROM)	1998 0-471-96936-2 $84.00 Kolman	www.wiley.com/WileyCDA n.a. n.a. n.a.

Note: This paper identifies SOPs by this abbreviation.

Pages, Words & SOPs

One relatively objective measure of the commercial products is their heft – the number of pages, words and SOPs. These measures are, however, not entirely straightforward. For example, the number of words per page and use of the words varies. The scope and depth of the SOPs also vary. SOP products should not be purchased by the pound.

Table 2: Pages, Words & SOPs

	Coach	CCRP	Morley	ResDyn[1]	MedTrials	Clive[2]	Kolman
Pages (Total)	290	184	324	105	113	270	177
Words (Total)	47,897	35,604	62,647	28,000	22,000	46,000	30,000
SOPs	20	23	80[4]	22	22	14	28
Pages (SOPs)	132	104	197	100	73	52	59
Words (SOPs)	34,671	22,070	45,250	26,000[3]	14,941	12,000[3]	13,000[3]
Words/ SOP	1,734	960	565	1,182	679	857	464

Notes:

1. Excludes extensive collection of regulations and guidelines.
2. Excludes 22 additional SOPs for IRBs, sponsors and CROs.
3. Estimated from a 5-page sample.
4. Includes 7 HIPAA and 11 gene therapy SOPs.

SOPs

Each commercial SOP product includes a subset of the 72 SOP topics listed in Table 3 on the next page. All 72 topics may not be necessary for a specific site, but would require purchase of all the SOP products or the addition of homegrown SOPs to meet specific needs. Customizations and additions should comply with FDA and ICH Good Clinical Practice.

Caution: The number of SOPs in Table 2 maps only loosely to the SOPs listed in Table 3.

Table 3: SOP Topics

Adverse Event Reporting	Gene Therapy Studies	Protocol Feasibility & Selection
Advertising for Study Subjects	Information Access Control	Quality Control & Audits
After-hours Coverage	Informed Consent Development	Randomization and Stratification
Clinical Procedures (Examples)	Insurance Coverage for Clinical Research Personnel	Randomization Code Breaking
Clinical Research Personnel CVs and Licenses	Investigational Drug Accountability, Storage, Dispensing and Return	Record Retention
Clinical Research Personnel Selection, Qualification, Responsibilities & Job Descriptions	Investigator Meetings	Recruiting Study Subjects
Clinical Research Personnel Training & Documentation	Investigator's Brochure	Regulatory Binder Set-up and Maintenance
Clinical Study Operations	IRB Communications & Documentation	Regulatory Files
Clinical Trial Agreement Amendments	Laboratory	Screening Study Subjects
Clinical Trial Budgets	Live Case/Photography in Device Study	Serious Adverse Event Reporting
Completing and Maintaining Case Report Forms	Live Case/Photography in Drug Study	Site Initiation Visits
Completion of FDA-1572	Managing Protocol Amendments	Site Monitoring Visits
Confidentiality of Clinical Trial Materials	Medicare Submissions	Site Qualification Visits
Data Collection	Misconduct and Fraud	Specimen Collection, Handling & Shipping
Delegation of Authority	Negotiating Clinical Trial Agreements	Sponsor & IRB-Initiated Audits
Disaster Recovery Planning	Nursing Procedures (Examples)	Sponsor/CRO Communications & Visits
eCRFs and Remote Data Capture	Obtaining & Documenting Informed Consent	Study Close-Out Activities
Electronic Records and Signatures	Obtaining and Maintaining IRB Approval	Study Contact Information
Equipment	Obtaining Informed Consent from Subjects Unable to Give Personal Consent	Study Files & Data Management
Estimation of Potential Subject Numbers	OSHA Guidelines	Study Organization and Planning
FDA Inspections	Preparation, Approval, Review and Maintenance of SOPs	Study Start-up
Financial Disclosure	Preparing and Managing Source Documents	Study Termination Visit
Foreign Language Consent	Protocol Deviations & Violations	Subject Management
IND Safety Reports	Privacy Practices & HIPAA Compliance	Subject Records

Organization

It is easier to find information in an SOP with numerous sections, but it takes additional effort to create and maintain the organization. Commercial SOPs are organized in 3 to 9 of the following 12 sections:

- **Administrative.** Author, approvals, numbering, revisions, next review date, etc.
- Background /Introduction. The "why" of the SOP
- **Purpose/Objective.** Essentially an elaboration of the title
- **Scope.** The types of activities and personnel to which the SOP applies.
- **Responsibility.** Who is responsible for performing the procedures; if different people (roles) are responsible for different parts of the procedures, can become redundant to the Procedures section
- **Process Overview.** A variation on Purpose/Objective
- **Procedures.** The "meat" of the SOP
- **References/Applicable Regulations and Guidelines.** Convenient for clarifying ambiguous situations
- **Related SOPs.**
- **Definitions.**
- **Attachments.**

Scope within Informed Consent SOPs

All SOP products have informed consent SOPs. Because of their importance, they presumably are among their authors' best efforts. Table 4, on the next page. lists 32 of the topics covered in informed consent and related SOPs. The SOP products cover 37% to 59% of the consolidated list.

Cautions: The consolidated list is not complete. It excludes many common topics and fine points. It does not describe the level of detail or the specific details within a topic, which vary widely. Words/SOP in Table 2 gives some indication of level-of-detail, but does not account for economy of expression.

Table 4: Informed Consent SOP Scope

	Coach	CCRP	Morley	ResDyn	MedTrials	Clive	Kolman
Informed consent is a process	x		x	x	x		
ICF development	x	x	x	x		x	
IRB special requirements	x					x	
ICF reading level	x		x			x	
IRB approval process	x	x	x	x		x	
Who can obtain consent	x		x	x	x	x	x
Person obtaining consent is knowledgeable							x
Vulnerable subjects	x			x	x		
Pediatric subjects		x	x		x	x	
Non-English speaking subjects	x	x			x	x	
Foreign language translation of ICF	x	x	x		x	x	
Illiterate subjects			x	x	x	x	
Legally-authorized representatives	x	x	x	x	x		x
Witnesses	x		x	x	x	x	x
Include friend or relative							x
Short form consent		x		x			
Signature and date requirements	x	x	x	x		x	x
File signed ICFs	x		x	x	x	x	
Copy of ICF to subject	x	x	x	x	x	x	
HIPAA authorization				x			
Attach state informed consent laws to SOP			x				
Documentation of consent	x	x	x	x			
ICF revisions	x	x	x	x	x	x	
Inform subjects of new information	x		x		x		
If legally-authorized consent, reconsent later			x				
Emergency exceptions		x		x			x
IRB waiver of need for informed consent	x			x		x	
No sedative or amnesiac within 4 prior hours			x				
Dealing with unsure subjects							x
If incorrect ICF version used						x	
TOTAL NUMBER	18	12	19	17	13	16	18

Supplemental Material

SOP products include a variety of supplemental material along with the SOPs, as set forth in Table 5. Table 6 presents more specific examples of supplemental materials for informed consent.

Table 5: Supplemental Material

	Coach	**CCRC**	**Morley**	**ResDyn**
Forms & Checklists	34	47	44	0
Citations	Yes	Yes	Yes	Yes
Acronyms	Yes	Yes	No	No (Free on website)
Definitions	Yes	Yes	Yes	Yes
Resources	References, web links	Links to government forms	Web links	Extensive collection of regulations and guidelines; Web links
Index	No	No	No	No
Other SOPs	Canadian Privacy ($600)	Privacy ($125), IRB ($2,500), & Sponsor (call for pricing) SOPs available separately	IRB ($799), Oncology Nursing Research ($60), Clinical Research Monitoring ($200) & Device Sponsors ($2,399) SOPs available separately	No

	MedTrials	**Clive**	**Kolman**
Forms & Checklists	10	17	57
Citations	Yes	Yes	No
Acronyms	No	No	Yes
Definitions	Yes	No	No
Resources	No	No	Summary of clinical trials; summary of regulations
Index	No	Forms only	Yes
Other SOPs	No	Also includes 9 IRB SOPs and 13 Sponsor/Monitor/CRO SOPs	No

Table 6: Informed Consent Supplemental Material

Background
FDA Guidelines for Obtaining Informed Consent
FDA Elements of Informed Consent
ICH Elements of Informed Consent
Sample Informed Consent Template
Assent of Children Form
Clarification of the Short Form
Informed Consent Checklist
Informed Consent for Subjects Unable to Give Personal Consent Checklist

Wording

SOP products express many of the same concepts, but in their own wording, and often with variations in content. For example, the bold text in Table 7 identifies what activities are prohibited prior to obtaining informed consent. None of the SOP products are very specific about the prohibited activities. For example, they do not define "screening procedures," so it is unclear what, if any, personal information may be gathered prior to obtaining informed consent.

Caution: Do not use this sample text to evaluate the products; a single out-of-context sentence is far too small and misleading a sample.

Table 7: Informed Consent Wording

Coach	Obtain all required signatures **prior to the subject's participation in the trial**.
CCRP	Note in the subject's records the date (and time) of informed consent, indicating that consent was obtained **prior to initiation of any screening procedures or study-related activities**.
Morley	Informed consent will be obtained for each research subject **prior to any screening procedure(s) or altering a subject's care for the purpose of research**.
ResDyn	Ensure that each informed consent form was signed and dated by the subject and the person obtaining the informed consent **prior to the study subject's participation in the study**.
MedTrials	Informed consent will be obtained for each research subject **prior to altering a subject's care for the purpose of research**.
Clive	The Investigator, Subinvestigator, Study Coordinator, or other delegate will explain the study to the potential subject **before any study procedures, including screening evaluations, are accomplished**.
Kolman	Written informed consent must be obtained **before any study-specific procedures are undertaken**.

Readability

Table 8 presents readability statistics for the SOP products, calculated by Microsoft Word. For reference, this paper has a reading ease score of 39.2 and a grade level score of 11.2.

Table 8: Readability

	Coach[3]	CCRP	Morley	ResDyn[3]	MedTrials	Clive[3]	Kolman[3]
Words/ Sentence	19.2	20.8	19.8	23.4	22.4	21.0	16.5
Characters/ Word	5.4	5.7	5.5	5.4	5.7	5.3	4.9
Flesch Reading Ease[1]	27.3	20.0	25.9	25.6	13.8	34.8	49.4
Flesch-Kincaid Grade Level[2]	12.0	12.0	12.0	12.0	12.0	12.0	10.4

Notes:

1. Flesch Reading Ease scores do not translate directly into Flesch-Kincaid Grade Level scores. Flesch Reading Ease = 206.835 – (1.015 x ASL) – (84.6 x ASW). Flesch-Kincaid Grade Level = (.39 x ASL) + (11.8 x ASW) – 15.59. (ASL = average number of words per sentence and ASW = average number of syllables per word)
2. Microsoft Word displays a maximum Flesch-Kincaid Grade Level score of 12.0.
3. Estimated from a 5-page sample

Cost

Commercial SOP products range in price by a factor of 14: from $84 to $1,200. In a perfect market, the prices should correlate with value, so one may conclude that the SOP market is not perfect, at least when judged by the objective measures in this paper. The most expensive product is not necessarily the best for all sites, nor is the least expensive necessarily the worst. Given the great value of SOPs and the substantial cost of writing/adapting and implementing good ones, price should be only one of many considerations in a purchase decision. Table 9, on the next page, presents prices and measures of cost.

Table 9: Cost

	Coach	CCRP	Morley	ResDyn	MedTrials	Clive	Kolman
Price	$1,200.00	$995.00	$625.00	$495.00	$350.00	$229.95	$84.00
$/SOP	$60.00	$43.00	$7.81	$22.50	$15.91	$16.43	$3.00
$/100 SOP Words	$3.46	$4.50	$1.39	$1.90	$2.34	$1.92	$0.65
$/Total Pages	$4.14	$5.13	$1.93	$4.71[1]	$3.10	$0.85[2]	$0.47

Notes:

1. Based on total number of pages, excluding government materials.
2. Based on total number of pages, including IRB and sponsor/CRO SOPs

Summary of Strengths

Each of the commercial SOP products has a unique set of strengths:

Coach provides detailed SOPs, compliant with Canadian regulations.

- Second-most total words, SOP words and SOP pages
- Most words per SOP
- Most detailed informed consent SOP (as measured by words)
- Online SOP course and exam expected in 2005
- Current (2004 copyright)
- FDA, ICH, Health Canada, and Canadian Tri-Council-compliant

CCRP offers highly-organized SOPs, accompanied by excellent forms.

- Most (47) forms and checklists
- Clear identification of who does what
- Consistent SOPs available separately for privacy, IRBs and Sponsors
- FDA and ICH-compliant

Morley's collection of 80 SOPs has the broadest scope and is the best value

- Most (80) SOPs
- Most total and SOP pages; most total and SOP words
- Most detailed informed consent SOP (as measured by topic)
- Second-most (44) forms and checklists
- Includes 7 HIPAA and 11 gene therapy SOPs
- Consistent SOPs available separately for IRBs
- Lowest cost per SOP and second-lowest cost per 100 SOP words
- FDA and ICH-compliant

Research Dynamics provides in-depth SOPs, accompanied by an extensive collection of regulations and guidelines.

- Includes over 400 pages of regulations and guidelines
- Current (2004 copyright)
- FDA and ICH-compliant

MedTrials delivers the essential SOPs with practical tips not always found in other products.

- Current (2004 copyright)
- FDA and ICH-compliant

Clive offers an affordable core set of investigative site SOPs, plus IRB and sponsor/CRO SOPs.

- Includes additional SOPs: 9 for IRBs and 13 for Sponsors and CROs
- Second-most readable
- Second-lowest price
- Current (2004 copyright)
- FDA and ICH-compliant

Kolman provides an inexpensive SOP starter kit. Its introduction to clinical research and relatively detailed background for each SOP are especially helpful to the novice investigator.

- Introduction to clinical research and summary of regulations
- Most (57) checklists
- Detailed background for each SOP
- Includes index
- Most readable
- Lowest price

A good collection of Standard Operating Procedures, along with an accompanying handbook, is a key ingredient for consistently high-quality clinical research. Commercial products can be very helpful in getting started or expanding the collection. Given that their cost is a small fraction of their value, no site should be without at least a basic set of SOPs.

Postscript: The Future of SOPs?

SOPs are useful only to the extent that they are incorporated into day-to-day activities. The Jacksonville Center for Clinical Research, a large multi-site investigator in Florida, is developing www.e-TrialDoc.com, an integrated, online solution for managing SOPs, forms, training and other document- and knowledge-management site activities. The SOPs are role-specific. For example, there are separate informed consent SOPs for the investigator and the coordinator. A search tool enables access to relevant SOPs. FAQs are also available. In the training and certification module, if a student is unable to answer a question in a quiz, he/she can link directly to the relevant SOP for review. The website is not yet a mature commercial product, but a few external sites have licensed it for their use. Subscription information is on the website.

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Norman M. Goldfarb is Managing Director of First Clinical Research, a provider of clinical research consulting, training, implementation and research services. He is also Chairman of the Model Agreement Group Initiative. He can be contacted at: (650) 465-0119, email: ngoldfarb@firstclinical.com.

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