EVERYTHING YOU WANTED TO KNOW ABOUT TRIAL MANAGEMENT...

NINDS Clinical Trials Methodology Course
15 September 2017
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Disclosures

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NINDS Clinical Trials Methodology Course
15 September 2017

**Trial Management Webinar Objectives:**

I. Improve knowledge of **design/conduct** of clinical trials in neurosciences
II. Analyze information presented
III. Integrate relevant content into trial **design/conduct**
Clinical Research Trial Management: Today’s Discussion

- Applicable to management of late-phase, interventional, federally-funded academic trials
  - Many aspects of trial management apply across all categories of trials
  - Research personnel on early Phase I and Phase II trials may also find content useful

- Real-life examples from POINT Trial
CLINICAL RESEARCH TRIAL MANAGEMENT
Trials are odd commodities to “manage”

- Clinical endeavors, dominated by clinical issues and typically led by people with clinical skills
  - Also time-bound “businesses” with two interdependent sets of processes: clinical and managerial
- Science alone can’t successfully deliver a trial
Trend toward more, larger and more complex global trials

Simple implementation and efficient management priorities

Same coordinated processes and systems required regardless of size, scope, costs or duration of trial

Source: https://ClinicalTrials.gov
Percentage of Registered Studies by Location
(as of September 12, 2017)

- U.S. only (36%)
- Non-U.S. only (47%)
- Not Provided (12%)
- Both U.S. and non-U.S. (5%)

Total N = 254,450 studies

Percentage of Recruiting Studies by Location
(as of September 13, 2017)

- U.S. only (38%)
- Non-U.S. only (57%)
- Both U.S. and non-U.S. (5%)

Total N = 44,512 studies

Source: clinicaltrials.gov
Clinical research trials can benefit from use of selected effective management techniques, systems and processes similar to those used to run successful business projects.
“Project management is a critical aspect of the clinical trial process whose importance in successful trial execution cannot be overstated.”

Source: J. Rick Turner, PhD, DSc, FASH, FACC
Defining the Trial as a Project

► A **concrete, organized** and **temporary** endeavor with **specific phases**, designed to produce a **unique product**, **service** or **result**

► Has a **defined beginning and end** (usually time-constrained, and often constrained by funding/deliverable) with **constant monitoring**

► Undertaken to meet **pre-determined goals and objectives**, typically to bring about **beneficial change** or **added value**

► **Consumes resources** (e.g., people, cash, materials, time)

Source: Project Management Institute
Typical approach to trial management uses protocol lifecycle as organizing principle.

Moves from start to finish in series of different steps in order to execute protocol.

Source: Harvard NCI
Project Management for Clinical Trials: Five Phases

- Project Closeout
- Project Initiation
- Performance Monitoring and Cost Control
- Requirements Definition and Planning
- Project Execution

Source: Project Management Institute
Trial Management Steps

1. Creation
2. Submission
3. Review
4. Activation
5. Conduct
6. Oversight
7. Publication
8. Closeout

Project Management Phases

- Project Closeout
- Project Initiation
- Performance Monitoring and Cost Control
- Requirements Definition and Planning
- Project Execution
5 Phases of Project Management

1. Initiating
2. Planning
3. Executing
4. Monitoring and Controlling
5. Closing

- Linked by results each phase produces
- Overlapping activities
- Interaction across phases
- Phase-specific inputs, tools, techniques, deliverables
**Trial Management: Initiating**

Key elements include:

- Define initial scope
- Identify stakeholders and sponsor
- Outline protocol hypothesis
- Draft consent form templates
- Identify patient population...

Conduct feasibility study(s)
Clinical trial feasibility: process of evaluating possibility of conducting a particular clinical program/trial in a particular geographical region with overall objective of optimum project completion in terms of timelines, targets and cost
Trial Management: Initiating Types of Feasibility Analysis

1. Program – broad based, e.g., disease prevalence in region(s) under consideration
   - Epidemiology plays important role

2. Study – more customized; considers clinical, regulatory, technical and operational aspects of specific countries/regions
   - Increase in site selection databases and predictive metrics

3. Site/investigator – “Micro-feasibility”: investigator and site competency, infrastructure, past performance in trials
   - 10% of sites over-perform, 10% under-perform
Trial Management: Initiating

- Most trials run late by 6+ weeks; less than half meet enrollment goals
  - 15-20% sites never enroll a single patient
- Ensures realistic assessment and capability to conduct trial
  - Considers clinical, regulatory, technical and operational aspects
- Feasibility study does not guarantee successful trials (and cost time and money) but can increase chance of study success
Trial Management: Planning

Business Plan

- Executive Summary
- Mission Statement
- Company Background
- Product Description
- Marketing Plan
- SWOT Analysis
- Competitor Analysis
- Operations
- Financial planning
- Timeline
Trial Management: Planning

- Make a comprehensive project plan...and use it!
- Use structured approach
- Include objectives, activities, timelines, resources, risks, metrics, communications, dependencies, contingencies
- Estimate costs and budget

### Gantt Chart for Start-up Phase of Global Clinical Trial

<table>
<thead>
<tr>
<th>Track Name</th>
<th>Country</th>
<th>Duration</th>
<th>Start</th>
<th>Finish</th>
<th>Predecessors</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Study Start Date</td>
<td></td>
<td>0 days</td>
<td>Tue 6/6/06</td>
<td>Tue 6/6/06</td>
<td></td>
</tr>
<tr>
<td>2. Feasibility Study</td>
<td></td>
<td>276 days</td>
<td>Tue 6/6/06</td>
<td>Tue 6/26/07</td>
<td></td>
</tr>
<tr>
<td>143 Sponsor Approves Sites for Qualification</td>
<td></td>
<td>256 days</td>
<td>Tue 7/26/07</td>
<td></td>
<td></td>
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<tr>
<td>268 Sponsor provides study documents for EC Submission</td>
<td></td>
<td>148 days</td>
<td>Tue 6/6/06</td>
<td>Thu 12/28/06</td>
<td></td>
</tr>
<tr>
<td>272 Qualification Visit Report</td>
<td></td>
<td>225 days</td>
<td>Thu 5/12/06</td>
<td>Wed 5/24/07</td>
<td></td>
</tr>
<tr>
<td>398 Qualification Visit Report</td>
<td></td>
<td>241 days</td>
<td>Thu 5/28/06</td>
<td>Thu 7/24/07</td>
<td></td>
</tr>
<tr>
<td>518 Sponsor Approves Sites</td>
<td></td>
<td>202 days</td>
<td>Thu 5/28/06</td>
<td>Fri 7/6/07</td>
<td></td>
</tr>
<tr>
<td>619 Translation, revision, and local automation of Regulatory Documents</td>
<td></td>
<td>91 days</td>
<td>Mon 11/6/06</td>
<td>Mon 3/12/07</td>
<td></td>
</tr>
<tr>
<td>639 Spanish</td>
<td></td>
<td>50 days</td>
<td>Mon 11/6/06</td>
<td>Fri 1/12/07</td>
<td></td>
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<tr>
<td>640 Protocol (version 04 Oct 2006)</td>
<td></td>
<td>26 days</td>
<td>Wed 12/6/06</td>
<td>Wed 1/12/07</td>
<td>269</td>
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<tr>
<td>641 CIF</td>
<td></td>
<td>29 days</td>
<td>Tue 12/5/06</td>
<td>Fri 1/12/07</td>
<td></td>
</tr>
<tr>
<td>642 Colombia (version 1.0) 12 Dec 2006</td>
<td>Colombia</td>
<td>29 days</td>
<td>Tue 12/5/06</td>
<td>Fri 1/12/07</td>
<td>270</td>
</tr>
<tr>
<td>643 Peru (version 1.0) 27 Dec 2006</td>
<td>Peru</td>
<td>17 days</td>
<td>Tue 12/5/06</td>
<td>Wed 12/27/06</td>
<td>220</td>
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<tr>
<td>644 Venezuela (version 1.0) 13 Dec 2006</td>
<td>Venezuela</td>
<td>19 days</td>
<td>Tue 12/5/06</td>
<td>Fri 12/29/06</td>
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<tr>
<td>645 Investigator’s Brochure (version 12 of 10 Oct 2006)</td>
<td></td>
<td>11 days</td>
<td>Mon 11/6/06</td>
<td>Mon 11/20/06</td>
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<tr>
<td>646 Amendment Investigator’s Brochure (amendment # 1-19 Oct 2006)</td>
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<td>Mon 11/20/06</td>
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<tr>
<td>647 Portuguese</td>
<td></td>
<td>91 days</td>
<td>Mon 11/6/06</td>
<td>Mon 3/12/07</td>
<td></td>
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<tr>
<td>653 Sponsor provides documents for MCH</td>
<td></td>
<td>221 days</td>
<td>Tue 6/6/06</td>
<td>Thu 4/10/07</td>
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<tr>
<td>671 IRB Preparation &amp; Release per site</td>
<td></td>
<td>210 days</td>
<td>Thu 10/9/06</td>
<td>Wed 8/8/07</td>
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<td>275 Sites send documents for IEC/REC site approval</td>
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<td>160 days</td>
<td>Fri 11/16/06</td>
<td>Thu 6/21/07</td>
<td></td>
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<tr>
<td>276 IEC Site Submission/Approval</td>
<td></td>
<td>215 days</td>
<td>Thu 11/16/06</td>
<td>Wed 11/14/07</td>
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<tr>
<td>813 Sites submit documents to EEC</td>
<td></td>
<td>259 days</td>
<td>Fri 15/06</td>
<td>Wed 12/25/07</td>
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<tr>
<td>914 Local Ethics Committee Submission/Approval</td>
<td></td>
<td>225 days</td>
<td>Fri 11/16/06</td>
<td>Wed 10/10/07</td>
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<tr>
<td>1013 First Site Approved by Local Ethics Committee</td>
<td></td>
<td>47 days</td>
<td>Thu 11/16/06</td>
<td>Thu 11/15/07</td>
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<tr>
<td>1018 COREP submission/approval (Brazil, when applicable)</td>
<td></td>
<td>121 days</td>
<td>Wed 11/10/07</td>
<td>Wed 12/10/07</td>
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<tr>
<td>1021 Sponsor provides drug labels</td>
<td></td>
<td>176 days</td>
<td>Tue 6/6/06</td>
<td>Tue 2/5/07</td>
<td></td>
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<tr>
<td>1026 Contract service provider approves drug labels</td>
<td></td>
<td>12 days</td>
<td>Mon 2/5/07</td>
<td>Tue 2/20/07</td>
<td></td>
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<tr>
<td>1031 Ministry of Health Protocol and first site submission</td>
<td></td>
<td>90 days</td>
<td>Wed 1/10/07</td>
<td>Tue 5/15/07</td>
<td></td>
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<tr>
<td>1039 Protocol and First Site Approved by Ministry of Health</td>
<td></td>
<td>144 days</td>
<td>Wed 2/8/07</td>
<td>Mon 9/12/07</td>
<td></td>
</tr>
</tbody>
</table>

Source: Prolific International

**Figure 1.** Chart includes a description of tasks and their predecessors, countries involved, and duration of activities.
POINT Trial Organization

**Advisory Committee**

**Executive Committee**

**Data Safety and Monitoring Board**

**POINT Trial Principal Investigators**
- Clay Johnston, MD, PhD: Principal Investigator
- Don Easton, MD: co-Principal Investigator

**UCSF Clinical Coordinating Center (CCC)**
- Clay Johnston, MD, PhD: Director
- Mary Farrant, MBA, RN: Project Director

**NETT Statistics and Data Management Center (SDMC)**
- Yuko Palesch, PhD: Director

**POINT CRC**
- Anne Lindblad, PhD: Director

**NINDS NETT**
- Bill Barsan, MD: Director

**Clinical and Logistical Aspects**
- Mary Farrant, MBA, RN: UCSF CCC Project Director

**Data Management**
- Catherine Dillon

**Statistics (Blinded)**
- Yuko Palesch, PhD

**Statistics (Unblinded)**
- Jordan Elm, PhD

**Enrollment**

**Outcomes**

**QA**

**Adjudication Packets**

**Enrollment Outcomes QA**

**Adjudication Packets**

**Clinical and Logistical Questions**

**Net Data**

**Central**

**Local**

**Oversight**

**Trial Management Model**
**Trial Management: Planning**

Make task-specific project plans whenever appropriate

<table>
<thead>
<tr>
<th>Task Status</th>
<th>Task</th>
<th>Task Name</th>
<th>Quoted Cost</th>
<th>Predecessors</th>
<th>Duration</th>
<th>Start</th>
<th>Finish</th>
<th>Actu Com Date</th>
<th>Risks / Issues / Opportunities</th>
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<td>X</td>
<td>TEC1210766 R7 A22</td>
<td>$0.00</td>
<td>113 days</td>
<td>Fri 9/1/17</td>
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<tr>
<td>-</td>
<td>Project Management</td>
<td>$0.00</td>
<td>1 day</td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>-</td>
<td>Issue component order form</td>
<td>$0.00</td>
<td>2 days</td>
<td>Fri 9/1/17</td>
<td>Fri 9/1/17 NA</td>
<td></td>
<td></td>
<td></td>
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<td>-</td>
<td>Procurement</td>
<td>$0.00</td>
<td>56 days</td>
<td>Fri 9/1/17</td>
<td>Fri 11/17/17 NA</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>-</td>
<td>Procurement of Clopidogrel</td>
<td>$0.00</td>
<td>10 days</td>
<td>Mon 10/2/17</td>
<td>Fri 10/13/17 NA</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>-</td>
<td>Procurement of Opiday</td>
<td>$0.00</td>
<td>10 days</td>
<td>Mon 11/6/17</td>
<td>Fri 11/17/17 NA</td>
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<td></td>
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<tr>
<td>-</td>
<td>Procurement of Excipients</td>
<td>$0.00</td>
<td>10 days</td>
<td>Thu 9/1/17</td>
<td>Thu 9/1/17 NA</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>-</td>
<td>Procurement of Components</td>
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<td>10 days</td>
<td>Mon 9/1/17</td>
<td>Fri 9/1/17 NA</td>
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<tr>
<td>-</td>
<td>Receiving</td>
<td>$0.00</td>
<td>51 days</td>
<td>Fri 9/1/17</td>
<td>Fri 11/24/17 NA</td>
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<tr>
<td>-</td>
<td>Receipt and reconciliation of Clopidogrel Commercial</td>
<td>$0.00</td>
<td>7 days</td>
<td>Mon 10/16/17</td>
<td>Tue 10/24/17 NA</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>-</td>
<td>Receipt and Reconciliation of Excipients</td>
<td>$0.00</td>
<td>7 days</td>
<td>Fri 9/1/17</td>
<td>Mon 9/25/17 NA</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>-</td>
<td>Receipt of Opiday</td>
<td>$0.00</td>
<td>5 days</td>
<td>Mon 11/20/17</td>
<td>Fri 11/24/17 NA</td>
<td></td>
<td></td>
<td></td>
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<td>-</td>
<td>Release of excipients</td>
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<td>Tue 10/3/17</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>-</td>
<td>Receipt and release of components</td>
<td>$0.00</td>
<td>5 days</td>
<td>Mon 9/1/17</td>
<td>Fri 9/22/17 NA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-</td>
<td>Labels</td>
<td>$0.00</td>
<td>44 days</td>
<td>Fri 9/16/17</td>
<td>Wed 11/15/17 NA</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>-</td>
<td>Booklet Labels</td>
<td>$0.00</td>
<td>44 days</td>
<td>Fri 9/16/17</td>
<td>Wed 11/15/17 NA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-</td>
<td>Issue/Receipt of text (UTF) or labels</td>
<td>$0.00</td>
<td>5 days</td>
<td>Fri 9/15/17</td>
<td>Thu 9/22/17 NA</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>-</td>
<td>Receipt of Randomization / Material List</td>
<td>$0.00</td>
<td>3 days</td>
<td>Fri 10/6/17</td>
<td>Tue 10/10/17 NA</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>-</td>
<td>Printing and Receipt of Booklet Labels</td>
<td>$0.00</td>
<td>30 days</td>
<td>Fri 9/22/17</td>
<td>Wed 11/16/17 NA</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>-</td>
<td>Issue VDAF to customer</td>
<td>$0.00</td>
<td>2 days</td>
<td>Wed 10/25/17</td>
<td>Thu 10/25/17 NA</td>
<td></td>
<td></td>
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<td>Receipt of VDAF from customer</td>
<td>$0.00</td>
<td>2 days</td>
<td>Wed 10/25/17</td>
<td>Thu 10/25/17 NA</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>-</td>
<td>Create Material Numbers</td>
<td>$0.00</td>
<td>1 day</td>
<td>Wed 11/11/17</td>
<td>Wed 11/11/17 NA</td>
<td></td>
<td></td>
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</tbody>
</table>

**POINT Lot 7:** study drug procurement and manufacture
Trial Management: Planning

ORDER SUPPLIES

MANUFACTURE PBO DRUG

NEW SUPPLY AVAILABLE

PROCESS COMPLETED

PBO FORMULA DEVELOPMENT

RELEASE AND STABILITY

REPLACE EXPIRING DRUG

DEC 2015
Contract finalized.
Materials in place by mid-December.

LATE DEC 2015 - JAN 2016
Develop formula for PBO and corresponding methods.

LATE JAN 2016- EARLY FEB 2016
Manufacturing and bottling/labeling of study drug.

MAR 2016- APR 2016
Release and one month stability.
Purchase commercial CLO.

MAY 2016
Trigger for labeling and distribution.

MAY 2016
Remove expiring drug.
Restock depots (OUS) and Central Pharmacy (US).

MAY 31, 2016
Stop dispensing 90 days prior to expiration date.
Replacement of inventory completed.
Essentials Skills for Trial Manager

**Effective communication:** Number one skill of a successful trial/project manager

Interpersonal skills: Ability to lead a diverse team across various levels of leadership

Experienced and organized: Played active roles in management of multiple trials

Proactive: Anticipate potential issues with a clinical trial
Monitoring essential to acquisition of quality data

- Develop customized monitoring strategy (RBM)

Evaluate systems in place and measure trial performance based on protocol/project plan
RBM - Funnel Plot of Proportion of Subjects with SAEs by Active Site
Trial Management: Monitoring and Controlling
Trial Management: Closing

Process depends on study type and data management requirements

Typically includes:
- Closeout-visit
- Data cleaning
- DBL
- Final analyses
- CSR
- Regulatory submissions
- Publication support

Schedule post-mortem
POINT CHALLENGES: Subject Accrual
POINT Challenges: Subject Accrual
POINT CHALLENGES: Premature Study Drug Discontinuation

Avoidable versus unavoidable reasons to discontinue study drug
Trial Management: 5 Tips

- Use project management techniques to supplement clinical trial approach
- Hire experienced trial manager
- Project, forecast, re-forecast and forecast again
- Automate
- Communicate
Trial Management: Resources

Project Management Journal®
https://www.pmi.org/learning/publications/pm-network

International Journal of Project Management
https://www.journals.elsevier.com/international-journal-of-project-management

UK Trial Managers Network
http://www.tmn.ac.uk/
**Trial Management: Resources**

Lawrence M. Friedman, Curt D. Furberg, David DeMets

**Pharmaceutical and Biomedical Project Management in a Changing Global Environment.** 1st Edition, 2010  
Scott D. Babler, Sean Ekins

**Project Management: A Quick Start Beginners Guide For Easily Managing Projects.** July 2017  
Susan Hollister
QUESTIONS?