Introducing “Essential Elements of Ethics”

A Systematic Method for Ensuring Key Ethical Issues Have Been Incorporated into Your Protocol

2013 PRIM&R Advancing Ethical Research Conference
Agenda

MRCT Introduction and Background, Rebecca Li

Protocol Ethics Guidance Work Group, David Forster & Susan D’Amico
  • Essential Elements
  • Protocol Survey

Essential Elements & Points to Consider Tool, Maeve Luthin
Collaborating to Improve Multi Regional Clinical Trials

Agenda

MRCT Introduction and Background, Rebecca Li

Protocol Ethics Guidance Work Group, David Forster & Susan D’Amico
  • Essential Elements
  • Protocol Survey

Essential Elements & Points to Consider Tool, Maeve Luthin
Collaborating to Improve Multi Regional Clinical Trials

The MRCT Center’s Purpose is… To improve the design, conduct, and oversight of multi-regional clinical trials, especially trials sited in or involving the developing world; to simplify research through the use of best practices; and to foster respect for research participants, efficacy, safety and fairness in transnational, trans-cultural human subjects research.

Objectives
Initiated by Trial Sponsors, the MRCT Center is a Partnership for Leaders

It is rare to have a moment when so many stakeholders within an industry have expressed public commitment to sharing information and building new standards for an entire industry – and to do so not only within industry, but in partnership with academia, non-industry research sponsors, and professional and lay communities around the world.

The MRCT learning community traverses boundaries of many kinds...
The MRCT Center Applies Its Core Values to All Projects

**Respect and Professionalism**
- Respect people, efficacy, safety and fairness
- Professional conduct of all those engaged in human research studies
- Leadership and management of the initiative by a qualified party that has no conflicting financial or clinical research interests

**Collaboration & Transparency**
- Authentic, substantive partnership with individual leaders, non-governmental organizations, researchers and industry employees who live and work in the developing world
- Sharing best practice ideas and learning across private sponsors of clinical research, where such sharing is legal and appropriate
- Transparent disclosure to the public of our work

**Quality & Continuous Improvement**
- A broad and representative process for identifying best practices and studies/assessments/evaluations to investigate the worth of those practices
- Peer review of proposals submitted both by work groups from within this initiative and by others
- Sufficient technical assistance for piloting and evaluating innovations
MRCT Center at Harvard is Uniquely Poised

• Housed at Harvard but shared ownership with Industry and other participants, including all goal setting and prioritization of work.
• A strong focus on ethics and ethical approaches to globalization, rather than regulatory reform or efficiency, per se.
• Participation by a broad range of sponsors, universities, EC/IRBs, academics, NGOs, and industry partners.
The MRCT Center’s Current Focus Areas

- Investigator Training
- Data and Safety Monitoring
- Ethics Guidance and Support
- Clinical Data Sharing & Transparency
- Global Regulatory Engagement
Initiated by Pfizer, the MRCT Project began with a Summit Meeting in July 2009.

Published a report of recommendations and opportunities for future work (PHASE 1 REPORT).

MRCT Center launch at Harvard

- Center staffed
- 3 working groups launched
- Global regulators engaged
- PI Training and Certification Symposia September 2012

- 4 working groups established and meeting milestones
- Pilot DSMB international fellow training (May 2013)
- Data Sharing Conference (May 2013)
- Meeting with Indian regulators (July 2013)
MRCT Center Implementation Strategy

- Identify Initiatives:
  - Impact
  - Significance
  - Expertise
  - Actionable

- Form Working Groups:
  - Global Diversity
  - World-class experts
  - Enthusiastic leaders
  - Deliverables / timeline

- Pilot Solutions:
  - Real world testing
  - Pre-determined metrics for success

- Implementation / Adoption:
  - Dissemination
  - Publication strategy
  - Roll out at partner organizations
Collaborating to Improve Multi Regional Clinical Trials

Agenda

MRCT Introduction and Background, Rebecca Li

Protocol Ethics Guidance Work Group, David Forster & Susan D’Amico
  • Essential Elements
  • Protocol Survey

Essential Elements & Points to Consider Tool, Maeve Luthin
Impact:

1. Limitations on current systems for reviewing trials regarding:
   - Effectiveness - quality of the review and ability to detect ethical problems
   - Efficiency – time for protocol review
   - Expertise - in some regions, local ECs lack the level of expertise or sufficient resources required to review complex protocols

2. Study teams developing protocols may not have a rigorous methodology to ensure that all ethical issues have been considered and addressed.
Co-chairs: DAVID FORSTER (WIRB), SUSAN D’AMICO (Abbvie),
Amy Davis (PRIM&R)
Kate Heffernan (Verrill Dana LLP)
John Isidor (Human Subject Protection Consulting)
Rebecca Li (MRCT)
Maeve Luthin (PRIM&R)
Holly Lynch (HLS - Petrie Flom)
Lindsay McNair (WIRB Copernicus)
Jennifer Miller (Bioethics International)
Jacquelyn Murphy (MRCT)
Luann Van Campen (Eli Lilly)
Mary Wacholtz (Johnson & Johnson)
Marc Wilenzick (MRCT)
Delia Wolf (HSPH)
Mark Barnes (ad-hoc) MRCT
Barbara Bierer (ad-hoc) MRCT
Protocol Ethics Working Group

David Forster, WIRB    Susan D’Amico, AbbVie

Building a Learning Community among Key Stakeholders
## Impact: Improved investigator/monitor quality and regulatory compliance with a focus in emerging countries

<table>
<thead>
<tr>
<th>Status</th>
<th>Deliverables</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete</td>
<td>Develop “Points-to-Consider” document, which provides further detail about “Essential Elements for Ethics” and guides the user towards drafting a standardized protocol and ICF ethics section</td>
</tr>
<tr>
<td>Complete</td>
<td>Perform validation survey of 100 protocols from academia, central IRBs and publications for presence/absence of Essential Elements</td>
</tr>
<tr>
<td>Launch November 7 2013</td>
<td>Collaborate with PRIM&amp;R to develop an on-line, publicly available tool kit and reference document that provides guidance at the main decision points during the study design phase, allowing users to address “Points-to-Consider” within a prescribed template format</td>
</tr>
<tr>
<td>Next Steps</td>
<td>Develop companion checklist for ECs to ensure that key ethics issues have been addressed</td>
</tr>
</tbody>
</table>
Goal: Develop key elements that are recommended for inclusion in multi-regional clinical trial protocols
Timeline

July 2012 – Team launched with diverse stakeholders from industry, CROs, academia

January 2013 – Eleven “Essential Elements” chosen and finalized to provide guidance on addressing key ethical questions

June 2013 – Team finalizes all Essential Element sections, including detailed “Points to Consider”, Examples and References

March 2013 – MRCT partners with PRIM&R for online hosting of the user-friendly Essential Elements Tool Kit and Reference Document

September 2013 – Protocol Survey validation effort completed
Eleven Essential Elements

1. Addressing Relevant Question
2. Choice of Control and Standard of Care
3. Choice of Study Design
4. Choice of Subject Population
5. Potential Benefits and Harms
6. Informed Consent
7. Community Engagement
8. Return of Research Results and Management of Incidental Findings
9. Post Trial Access
10. Payment for Participation
11. Study Related Injury
Background:
For a research study to be ethical, it must have scientific and social value and contribute to medical knowledge, meaning that it must be an “Evaluation of a treatment, intervention, or theory that will improve health and well-being or increase knowledge.”

Ethical Issue:
Without anticipated social value, human research participants are subjected to research risks without potential benefit to them or others.
2. Choice of Control and Standard of Care

**Background:**
Choice of control affects multiple aspects of the trial, including its ethical acceptability. When evaluating the ethics, it’s important to do so from the perspective of three control categories: Active comparator, placebo-alone, and placebo-in-combination, e.g. with background standard of care or in combination with active comparator.

**Ethical Issue:**
It is necessary to consider the standard of care otherwise available to the subjects, because all of the arms of a study will judged against the standard of care that subjects would receive if not enrolled in the research.
3. Choice of Study Design

Background:
The chosen study design(s) may be standard and well established for the question to be examined. The protocol should always lay out the details of the design, the specific assessments and their timing, the plan to manage risk, and the outline of the plan for analysis. However, new or exceptional issues of scientific validity or risk should be addressed.

Ethical Issue:

• Is the study design adequate to give useful information about the question asked (scientific validity)?

• Is what is asked of the individual subject reasonable and ethical?
4. Choice of Subject Population

**Background:**
Subjects in clinical studies are often exposed to risk and inconvenience that they would not otherwise experience. If the subjects represent a well-studied group for whom the risks including the safety profile have been well-defined, the specific choice of subject group may require no explanation beyond the scientific rationale. However, vulnerable populations* (who may either be at greater risk or may lack autonomy or capacity to directly consent to the research), and other populations who are not necessarily “vulnerable” may present special challenges.

**Ethical Issue:**

- Is the principle of fair distribution of benefit and risk met?
- Are vulnerable populations included? Why is this ethically acceptable?
  *e.g., children, adults without capacity, pregnant women, prisoners, economically disadvantaged, other vulnerable subjects*
5. Potential Benefits and Harms

**Background:**
Every protocol should provide sufficient information to allow assessment of whether there is a reasonable balance of benefit and risk.

**Ethical Issue:**

- Are interventions that may provide benefit at least as advantageous as available alternatives? (CIOMS 2002)

- If there is no direct benefit to the individual, are the risks reasonable and balanced by the benefit to society and the knowledge to be gained?
6. Informed Consent

**Background:**
Obtaining participants’ informed consent must follow local legal requirements and incorporate local cultural standards. Researchers must communicate the material information about the study, the benefits, and the risks, to potential participants to initiate the informed consent dialogue.

**Ethical Issue:**
Especially when the study involves a target population that is likely to have difficulty understanding the benefits and risks or consequence of participating in the trial, such as when study participants are children or do not have capacity to consent, the Sponsor should consider alternative ways to help communicate pertinent information.

Protocols should describe this process especially if there is a significant potential for coercion or undue influence of study subjects.
7. Community Engagement

**Background:**
Community engagement is the process of working collaboratively with groups of people in the development and conduct of research who are affiliated by geographic proximity, special interests, or similar situations with respect to issues affecting their well-being.

**Ethical Issue:**
Research guidelines are increasingly emphasizing the importance of collaborating, engaging and partnering with host communities (as well as with local investigators and policy makers) when conducting research in developing countries.

The central aim of this practice is to minimize exploitation by ensuring that a developing country determines whether the proposed research is acceptable and responsive to the community’s local health problems.

One of the largest challenges to operationalizing this principle is that there is no consensus definition for the term community.
8. Return of Results and Management of Incidental Findings

**Background:** This element seeks to identify prospectively what governing principles will be with respect to communicating both individual and general/aggregated research results to participants (or if not, what the justification is for not returning results), as well as encouraging investigators to think-through a management plan for any incidental findings that might be generated from the research.

**Ethical Issue:**

Return of Individual/General Research Results:
- Many ethics guidelines and regulations applicable to the conduct of human research recognize that participants may have a right to be informed, where appropriate, of the results of their participation and other significant information.
- The degree of that right (individual results, aggregated information, general progress report, etc.) and the scope of any duty on investigators to provide such results or act on them in the subject’s interest is currently variable.

Management of Incidental Findings (IFs):
- The possibility for IFs is increasing due to research with large data sets, including genomic sequencing.
- A clearly stated plan for how IFs will be managed (and what criteria, if any, would prompt reporting to the EC and/or utilization for clinical decision-making) may head-off ethical dilemmas.
**Background:**
Post trial access can be broadly defined as any sponsor-provided access to medical benefits after the study has ended. For instance, it could involve continued access to interventions found to be safe and effective in the research, or it could involve other types of medical benefits such as general health care interventions.

**Ethical Issue:**
Post trial access might be limited to those individuals who participated in the research, or it could be provided to a wider group such as all individuals affected with the disease being studied in a given region. Limitations and specifics should be provided so study participants are aware of what will happen once the trial is finished.
10. Compensation for Participants

**Background:**
Participation should be revenue neutral and subjects should be reimbursed for expenses. If subjects are to be paid for participating, this should be disclosed in the protocol and such information must be provided to subjects.

**Ethical Issue:**
Is compensation adequate to allow participation of groups that might be underrepresented?

- Is there “undue inducement”? If compensation beyond reasonable expenses is offered, how is this justified?
- Could the decision to participate be overly influenced by the compensation offered?
11. Compensation for Study-Related Injury

**Background:**
Adverse events are common in interventional trials and sometimes there is an injury to a trial participant. The informed consent process must clearly address whether medical care and compensation for injuries will be provided to participants, by whom, and under what circumstances.

**Ethical Issue:**
Clinical trials depend on the voluntary participation of the public and, in recognition of this relationship, ensuring that any injured participant has access to appropriate medical care and appropriate compensation for injury is an important ethical imperative for trial planning.

If compensation is limited, details must be prominently disclosed.
Protocol Ethics Essential Elements Survey

Objectives:
• To survey 100 clinical trial protocols for the presence/absence of the essential elements
• To provide verification of the current coverage of the elements in a sampling of protocols across industry, academia and government funded studies.

Trial Eligibility Criteria:
• International and Interventional
• Involving greater than minimal risk
• Each protocol included was “unique” meaning re-submissions or amendments of a protocol will not be included.
Protocol Ethics Essential Elements Survey

Methods:

• Protocols screened from four databases starting from June 1, 2013 and proceeding retrospectively

• Protocols evaluated by two reviewers* for presence or absence of the Essential Elements (binary evaluation).

• Inter-judge reliability tested with blinded collective scoring of Essential Elements of one protocol; high correlation resulted

*80% of protocols QC’d by second reviewer
## Participating Institutions

<table>
<thead>
<tr>
<th>Institution</th>
<th>Number of Protocols</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chesapeake IRB</td>
<td>20</td>
</tr>
<tr>
<td>Western IRB</td>
<td>20</td>
</tr>
<tr>
<td>Harvard (HSPH, HMS, HDS)</td>
<td>20</td>
</tr>
<tr>
<td>MRCT reviewed protocols from New England Journal of Medicine</td>
<td>40</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>100</strong></td>
</tr>
</tbody>
</table>
Protocol Survey Data Analysis

Demographics Collected:
• Funding Institutions
• Number of Countries
• Number of Participants

Essential Elements Coverage:
• By individual Essential Element across all 100 protocols
• Calculated per type of Funding Institution
• Calculated per Number of Countries listed in Protocol
• Calculated per Number of Participants listed in Protocol
Protocol Demographics

Funding Institution (n=100)

- Industry (57%)
- Government (32%)
- Academia (3%)
- Partnership (3%)
- Other (5%)
Protocol Demographics

Number of Countries (n=65)

- 1 country (43%)
- 2 countries (22%)
- 3-4 countries (20%)
- 5 or more countries (15%)
Protocol Demographics

Number of Participants (n = 97)

- 0-200 participants
- 201-400 participants
- 401-600 participants
- 601-800 participants
- More than 800 participants
## Results of Protocol Survey

<table>
<thead>
<tr>
<th>Essential Element</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Addressing Relevant Question</td>
<td>96</td>
</tr>
<tr>
<td>Choice of Control and Standard of Care</td>
<td>59</td>
</tr>
<tr>
<td>Choice of Study Design</td>
<td>44</td>
</tr>
<tr>
<td>Choice of Subject Population</td>
<td>39</td>
</tr>
<tr>
<td>Potential Benefits and Harms</td>
<td>76</td>
</tr>
<tr>
<td>Informed Consent</td>
<td>56</td>
</tr>
<tr>
<td>Community Engagement</td>
<td>9</td>
</tr>
<tr>
<td>Return of Research Results and Incidental Findings</td>
<td>49</td>
</tr>
<tr>
<td>Post Trial Access</td>
<td>22</td>
</tr>
<tr>
<td>Payment for Participation</td>
<td>40</td>
</tr>
<tr>
<td>Study Related Injury</td>
<td>43</td>
</tr>
</tbody>
</table>
# Results of Protocol Survey

<table>
<thead>
<tr>
<th>Essential Element</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Addressing Relevant Question</td>
<td>96</td>
</tr>
<tr>
<td>Choice of Control and Standard of Care</td>
<td>59</td>
</tr>
<tr>
<td>Choice of Study Design</td>
<td>44</td>
</tr>
<tr>
<td>Choice of Subject Population</td>
<td>39</td>
</tr>
<tr>
<td>Potential Benefits and Harms</td>
<td>76</td>
</tr>
<tr>
<td>Informed Consent</td>
<td>56</td>
</tr>
<tr>
<td>Community Engagement</td>
<td>9</td>
</tr>
<tr>
<td>Return of Research Results and Incidental Findings</td>
<td>49</td>
</tr>
<tr>
<td>Post Trial Access</td>
<td>22</td>
</tr>
<tr>
<td>Payment for Participation</td>
<td>40</td>
</tr>
<tr>
<td>Study Related Injury</td>
<td>43</td>
</tr>
</tbody>
</table>
Trends: Funding Institution

Average Percent of Essential Elements Covered by Type of Funding Institution

- Industry (n = 50) - 51%
- Government (n = 28) - 44%
- Academia (n = 3) - 18%
- Partnerships (n = 3) - 36%
- Other (n = 5) - 57%

[Bar chart showing the average percent of essential elements covered by different types of funding institutions]

0 10 20 30 40 50 60 70 80 90 100
Trends: Number of Countries

Average Percent of Essential Elements Covered by Number of Countries in Study

- 1 country (n = 28)
- 2 countries (n = 14)
- 3-4 countries (n = 13)
- 5 or more countries (n = 10)

- 1 country – 49%
- 2 countries – 40%
- 3-4 countries – 41%
- 5 or more countries – 45%
Average Percent of Essential Elements Covered by Number of Participants in Study

- 0 - 200 participants (n = 27)
- 201 - 400 participants (n = 15)
- 401 - 600 participants (n = 16)
- 601 - 800 participants (n = 5)
- 801+ participants (n = 34)
Conclusion

Among the 100 clinical trial protocols surveyed:

- The average protocol addressed 49% of the Essential Elements

- There was a large variation in coverage by specific Essential Element, ranging from 9%-96%.

- No substantive difference in coverage of Essential Elements based on type of funding institution, or number of countries or participants.

With an accessible and helpful tool, we could impact the inclusion of these Essential Elements in protocols and informed consent forms across studies run by industry, academia and government.
How could this Essential Elements Tool be used?

Guidance for study staff drafting protocols for PI initiated trials, government and industry studies

ECs & IRBs to encourage its use for …
- Complete consideration of ethical issues in clinical trials
- Efficient review of protocols for new investigators
- Development of internal checklist for protocol writers
Collaborating to Improve Multi Regional Clinical Trials

Agenda

MRCT Introduction and Background, Rebecca Li

Protocol Ethics Guidance Work Group, David Forster & Susan D’Amico
  • Essential Elements
  • Protocol Survey

Essential Elements & Points to Consider Tool, Maeve Luthin
What is it?

• An easily navigable document, divided into two parts and available in both PDF and Word formats.

• It guides users in thinking critically about ethical considerations that should be incorporated into protocols.

• Not all of the essential elements will apply to every protocol. In considering the applicable sections when drafting a protocol, users will be able to provide their IRBs and RECs with a better sense of the ethical issues within the proposed clinical trial.
Part I: The Tool Kit

The Tool Kit introduces each of the eleven essential elements and lays out the points to consider—a series of questions about each topic, the answers to which users may want to include in their protocol.
Part II: Reference Document

The Reference Document provides critical background information, examples, and references that more fully illustrate each of the essential elements.
Navigating the Document

• Users navigate the document by clicking on hyperlinks found at the top of each section and at the bottom of each page.

• The References and Additional Resources sections link to online versions of each of the citations.
Audience Feedback

1. Are there additional areas that we should address?

2. Are there suggested refinements of Essential Elements or Tool Kit/Reference Document?

3. Suggestions for focus groups of writers at different types of institutions?

4. Implementation suggestions?
Where can I find the Essential Elements?

The Essential Elements Tool Kit and Reference Document will be available as of November 8 on MRCT and PRIM&R websites:

http://mrct.globalhealth.harvard.edu/pages/resources

http://www.primr.org/
Click on “Knowledge Center”