SENSIBLE GCP – A PATIENT'S PERSPECTIVE

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May 4, 2012

Disclosure

- FightCRC accepts unrestricted grants from individuals, foundations and companies, including industry
- My affiliations:
  - NCI: protocol development and review committees; oversight of intramural program; oversight of extramural changes; DSMB
  - FDA: Patient representative program
  - CTTI: Executive committee
  - … and more

Patients are told:

1. You will make an informed choice about participating
2. Your safety will be monitored
3. You may or may not benefit from trial participation BUT …
   - **Your participation in the trial will benefit society**

1. You will make an informed choice about participating

- Informed consent process
- Informed consent document

European Forum for Good Clinical Practice

EFGCP Annual Conference 2012

Informed Consent – How Less Could Be More:

Effecting a paradigm shift so we do inform participants

24 & 25 January 2012

Résidence Palace, Brussels, Belgium

FIGHT COLORECTAL CANCER

get behind a cure.

MEDICINE

Informed consent on trial

Lengthy, complicated documents leave many clinical-trial participants in the dark about the risks they face.

"An influential group of ethicists and researchers warned ... that the process has become a box-ticking exercise focused **more on offering legal protection to a trial's organizer than actually protecting patients.**"

Nature, volume 482, 2-2-2012, p. 16

2. Your safety will be monitored

- AE / SAE reporting
- Monitoring

CTTI Project: Improving Reporting of Unexpected SAEs to IND Investigators

- Objective #4: Explore patients' expectations for how investigators should monitor and communicate information about product safety during the conduct of a clinical trial …

- Focus groups

Highlights of Results

- Thought investigators should be told about all SAEs immediately
- Had varied opinions about whether participants should be told about each unexpected SAE
- Thought practices for when and how participants are told should be updated to reflect modern communication methods (eg, email)
- Expressed serious concerns about financial conflicts of interest in monitoring and reporting SAEs

3. Your participation in the trial will benefit society

- GCP Principle #3: Risk Identification

  "Before research involving humans is initiated, foreseeable risks and discomforts and any anticipated benefit(s) for the individual trial subject and society should be identified."

- Research question is scientifically valid

When does society benefit?

- Well-designed, scientifically valid trial that …
- Accrues and retains patients and ..
- Results are analyzed and published and …
- Research results move the body of knowledge forward
  - Productive failure is an acceptable result

Accrual: Phase III Oncology

Trials activated	191
Estimated # (%) of trials with inadequate (<90%) accrual	43 (22 %)
Projected # patients accrued when trials are closed	176,627
Projected # patients on trials with inadequate accrual	2991 (1.7%)

Korn et al
Accrual Experience of National Cancer Institute Cooperative Group Phase III Trials Activated From 2000 to 2007
JCO Dec 10, 2010:5197-5201

Opening a Phase 3 Cooperative Group Trial Requires:

- 769 steps
- 36 approvals
- 2.5 years from formal concept review to study opening.
- “a strong negative statistical relationship between achievement of accrual goals and development time”

Dilts et al
Phase III Clinical Trial Development: A Process of Chutes and Ladders
Clin Cancer Res. 2010 November 15; 16(22): 5381–5389.

Phase II oncology trials

Publication of Phase II abstracts presented at American Society for Clinical Oncology in 1997, 1999 and 2001:

- 559 abstracts presented
- 60.8% were published

Reason for lack of publication:

- Uninteresting results
- Lack of time
- Relocation of authors

Hoeg et al
Publication outcomes of phase II oncology clinical trials
Am J Clin Oncol. 2009 Jun;32(3):253-7

Phase III oncology trials

Publication of Phase III abstracts presented at ASCO from1989 - 2003

- 709 phase III clinical trial abstracts
- 643 (91%) were followed by publication
- 66 remain un-published

Unpublished trial characteristics

- 36 (55%) were government-funded
- 32 (48%) were plenary or oral presentations

Reasons for not publishing

- Lack of time, funds or other resources
- Insufficient priority to warrant publication

Why does that matter?

23,770 patients participated in the unpublished trials

Compendium of unpublished phase III trials in oncology: characteristics and impact on clinical practice

Tam VC, Tannock IF, Massey C, Rauw J, Krzyzanowska MK.

J Clin Oncol. 2011 Aug 10;29(23):3133-9.

Challenges with CT.Gov dataset

- Missing, incomplete or incorrect data
- Lack of standardization in descriptions

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Califf et al

Characteristics of Clinical Trials Registered in ClinicalTrials.gov, 2007-2010

JAMA. 2012;307(17):1838-1847

Research results move the body of knowledge forward (sometimes)

Effort is being expended in investigating efficiency measures (i.e., **doing trials right**) through achievement of accrual and endpoint goals for clinical trials. It is time to assess the impact of such trials on meeting the critical needs of cancer patients by establishing effectiveness measures (i.e., **doing the right trials**).

The Importance of Doing Trials Right While Doing the Right Trials
David M. Dilts and Steven K. Cheng
Clin Cancer Res January 1, 2012 18; 3

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Evaluation of public portfolio

NCI Clinical Trials Strategic Subcommittee Objectives:

- Monitor and assess the balance, coherence and appropriateness of NCI's clinical trials portfolio.

….

- Monitor and assess other aspects of clinical trials operations across the system including collaboration and timeliness.

CTTI Clinicaltrials.Gov

Interventional trials registered between 2007 and 2010

- 62% enrolling 100 or fewer participants
- 66% were single center

Califf et al *JAMA. 2012;307(17):1838-1847*

Sensible GCP: Patient Perspective

Protect patients on trials

- Improve informed consent process
- Practice risk-based monitoring and meaningful reporting of adverse events
  - Don’t squander resources on meaningless oversight
- Improve the system
  - Survey patients as to satisfaction and use the results to improve the process

Protect society (1)

- Ensure that research is feasible (able to be completed)
- Require collaboration
  - Support cross-institution collaborations to develop phase 2 trials that will lead to meaningful phase 3 trials or produce productive failure
  - Don’t fund “siloed” research

Protect society (2)

- Focus on patient benefit and disease burden through portfolio management, especially with publicly-funded research
- Evaluate progress through changes in clinical practice and patient care

Transparency!

- **Require accurate and timely reporting of research and results to clinicaltrials.gov**
- **Post public report cards for any organization that conducts clinical research**
  - Patient satisfaction with research
  - Achievement of timelines and accrual goals
  - # inappropriate SAE reports
  - Quality of information provided to clinicaltrials.gov

Some promising signs

- FDA: risk-based monitoring, rational SAE reporting
- OHRP: improvements to the Common Rule to decrease ambiguity and reduce duplicative IRB review
- NCI: streamlining research systems; incentivizing collaboration
- NLM: improving data quality in CT.gov

Change is hard

- **Incentivize change**
  - Reward good behavior such as collaboration, accurate reporting to CT.gov and so on
- **Penalize non-performance**
  - Significant financial penalties
  - All trial sponsors – industry, academia

Talk doesn't cook rice

THANK YOU!