Regulatory Issues: Challenges from Recent Trials

Jackie Bosch

Sensible Guidelines Workshop

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Regulatory Issues

- Many have identified the issues
  - Investigators such as Dr.'s Neaton & Minisman; Sensible Guidelines Working Group (Duke, Oxford, McMaster)
  - Organizations, e.g. Institute of Medicine (IOM), European Science Foundation (ESF)
  - Governmental committees e.g. Organisation for Economic Co-operation and Development (OECD)
- Consistent identification of key problems….

The problems…..

1. Multiple "approval" layers:
   - At national and local levels
   - Need for separate import licenses
2. Varying requirements:
   - Difficult to determine exactly what is required; results in incorrect/incomplete submissions

The problems (con't)

3. Lack of clarity re: process:

- Options for follow up? discussion during review process? response once decision is made?

4. Over interpretation of requirements:

- Results in additional work
- Creates an environment of fear of "audit findings", rather than focus on most appropriate processes

5. Indemnification: How to cover when the sponsor is not a commercial entity industry?

Current solutions

- Exclude some countries from trials because of potential delays or rejection by reg auth
- Create complex and unique processes for each country to address (perceived?) regulatory demands
- Create the need for specialized knowledge such that the average investigator is not able to/interested in learning/taking the risk

Which result in…

- Fewer multinational, investigator initiated studies being conducted
- Increased costs:
  - Hiring additional companies to prepare and maintain submissions adds 3-4x to the study cost
- Increased delays – for both industry sponsored and investigator initiated studies

Start-up Process: Industry

Activity	Date to First	Avg Length (days)	IQ Range (days)
Protocol Finalized	2010-Feb-22		
Final Decision (FD) (clock starts)	2010-May-10	77	
Final Decision – Health Authority (HA) Submission	2010-Jul-25	171	101-211
HA submission – HA approval	2010-Jul-14	88	31-120
FD – Central Ethics Approval	2010-Jul-21	222	141-297
FD – Local Ethics Approval	2010-Jul-23	229	141-331
Eth Approval to First Participant Visit	2011-Jan-27	139	61-174
Time from FD to First Participant Visit	**2011-Jan-27**	**350**	**266-417**

Start-up Process: Inv Initiated

Timeline	Mean (mths)	Median (mth)	Range (min,max)
Final decision to reg submission	7.5	7	2-19
Reg submission to approval	5.7	5	1-15
Approval to start-date (first-pt-first-visit)	4.2	4	1-9
Final decision to first participant	**17.2**	**16**	**9-31**

Rathe et al., 2011

Then & Now

	1993	2012	
		IIS	IND
Final decision to reg approval	4 mos	12 mos	8 mos
Reg approval to first participant	2 wks	4 mos	4 mos

- Start-up time has at least doubled, longer if an investigator initiated study (IIS)
- No appreciable improvement in study conduct

Going Forward

- Harmonize & Simplify
  - Success in other fields (air traffic control, film for cameras, the internet), therefore possible
  - Field expert involvement – scientists & policymakers
  - Risk based approach to identify processes according to study (e.g. Phase 2 vs Phase 3 trials)
- National and international leadership required at all levels
- Ultimate goal: The entire approval process for all countries to take no more than 4 months - back to the future!