Ethical Considerations in Accelerated Approval

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Key Points

I. Efforts to shorten development and approval times to incentivize innovation raise unique ethical issues.

II. Important to consider the full range of ethical issues surrounding such efforts.

My Focus

I. Broad range of proposals to incentivize intervention development by compressing development and review timelines.
   1. Accelerated approval (surrogate markers for approval + post-marketing studies)
   2. Proposals for early access (e.g., after phase II).

Motivations

I. “Pull” for innovation. Reducing time to market shortens time to revenue and maximizes period of patent protection or market exclusivity.

II. Patients with few treatment options often willing to accept increased risks.

III. Stakeholder interests seem to be aligned!

Ethical Issues

I. Short development timelines in novel areas produce narrow "bandwidth" of information.[1]
   1. Indication
   2. Dose
   3. Timing and schedule

II. Clinical use of approved products often requires broader "bandwidth" of information.

[1]Jonathan Kimmelman and Alex John London, "The Structure of Clinical Translation: Efficiency, Information, and Ethics," *Hastings Center Report* 45 (2015): 1-7. DOI: 10.1002/hast.433

Ethical Issues

III. Collecting this information in clinical settings is less efficient than collecting it in development:

1. "Noisier" environment.
2. More patients exposed = more harms to locate boundaries.

Ethical Issues

IV. Costs of learning in development borne by developer while costs of learning in clinic are borne by patients and third-party payers.
    1. Shifting these costs raises questions of fairness
V. Market access decreases developer incentive to conduct post-marketing studies in a timely manner.

Ethical Issues

VI. Participants and patients may be willing to accept increased risk, but serious adverse events can have a chilling effect on development.[1]

1. Gelsinger death in gene therapy[2]
2. Fetal tissue in PD.

[1] Alex John London, Jonathan Kimmelman, Marina Elena Emborg. Beyond Access vs. Protection in Trials of Innovative Therapies. Science 328 (2010) 829-30.

[2]James M. Wilson. A History Lesson for Stem Cells. Science 342 (2009) 727-8.

Ethical Issues

VII. Market access and subsequent withdrawal divert scarce resources to ineffective or harmful interventions.

1. Shifts inefficiencies to the health care system.

VIII. Difficult to assess the costs of an erosion in trust in gatekeeper institutions.

Conclusion

I. Patient/participant tolerance for risk is only one ethical concern among many.

II. Development is more protracted in areas where knowledge of causal structures is underdeveloped.

   1. More false positives in small studies
   2. More exploratory work needed to identify therapeutic window

III. Development and approval timelines may not be appropriate targets for incentives.