POSSIBILITIES FOR HARMONIZATION OF REIMBURSEMENT (HTA) AND REGULATORY PROCESSES AND EVIDENTIARY REQUIREMENTS IN CANADA

Moderator: Ron Goeree

Panelists: Michael Drummond, Chris Henshall, Barbara Sabourin, Chander Sehgal, Bernice Tsoi
Existing Paradigm in Obtaining Market Access

Pre-market Space

- Discovery + Ideation
- Invention + Prototyping
- Preclinical
- Clinical
- Regulatory Decision

Class I & II Devices
- Market Authorization
- Class III & IV Devices; Drugs

Post-market Space

- Product Launch
- Post-market Monitoring
- HTA
- Advocates/Stakeholders

- Relative efficacy/effectiveness
- Economic and budget impact
- Unknown: may/ may not be evidence-based

Assessment Focus

Key Stakeholders

- Industry/Manufacturers
- Regulators
- Payers

- Quality, safety, efficacy
- Risk-benefit profile

Market Access?
Current Paradigm

Criticism of Existing Paradigm

- Disjointed and poor alignment between regulatory and HTA (reimbursement) processes

- This has resulted in:
  - Delayed patient access
  - Inefficiencies that are time- and resource- intensive:
    - Dual clinical development track
    - Duplicated, sequential assessment
  - Increased uncertainty for manufacturers:
    - Different decisions between regulators and payers
Great Line Up of Speakers

- Bernice Tsoi (McMaster University)
  - HC Research Project Perspective
- Chris Henshall (University of York, UK)
  - Findings from HTAi Policy Forum
- Barbara Babourin (Health Canada)
  - Regulatory Perspective
- Chander Sehgal (CADTH)
  - HTA Perspective
- Michael Drummond (University of York, UK)
  - EU Perspective
HARMONIZATION: SYSTEMATIC REVIEW AND QUALITATIVE INTERVIEWS

Bernice Tsoi
Programs for Assessment of Technology in Health (PATH) Research Institute
McMaster University
Acknowledgements

- This work was done by: Lisa Masucci, Kaitryn Campbell, Daria O’Reilly, Mike Drummond and Ron Goeree

- Funding from this study was provided by Health Canada. The views presented here are solely of the presenters and do not necessarily reflect official views of Health Canada.
Objectives & Methods of Our Study

➢ To identify and evaluate proposed and existing strategies to harmonize regulatory and HTA/reimbursement activities, in particular identifying the key barriers and facilitators to such initiatives

➢ **Method:**

   Two-parts:

   1. Systematic literature review
   2. Key informant semi-structured interviews
Systematic Literature Review Results

- **Systematic Review:**
  - 17 = theoretical discussion
  - 46 = empirical examples*
    - Jurisdictions/ countries: Australia, Canada, Europe, United Kingdom, United States, Sweden, Singapore, international

*NOTE: 3 papers provided both a theoretical and empirical discussion
Four Theoretical Frameworks to Harmonization

- The following strategies were identified with an intent in harmonizing HTA-regulatory processes:
  1. Alignment of evidentiary needs
  2. Early tri-partite dialogue
  3. Parallel submission
  4. Adaptive licensing

- In reality, these are not mutually exclusive
Taxonomy of Approaches to Harmonization

Evidentiary Needs
- Alignment of Evidentiary Needs
- Early Tripartite Dialogue
- Pre-market evaluation

Processes & Timeframes
- Parallel Submission
- Adaptive Licensing

PASSIVE
ACTIVE
Qualitative Interview Results

Flow chart of participant inclusion in qualitative interviews

- Individuals contacted (n=18)
- No response (n=4)
  - U.S. Academic (n=1)
  - European Academic (n=1)
  - European Regulator (n=1)
  - European HTA-representative (n=1)
- Individuals responded (n=14)
- Individuals interviewed (n=14)

Countries Represented by the Respondents

- Canada (57%)
- US (15%)
- UK (14%)
- Netherlands (7%)
- International (7%)

Roles of Respondents

- HTA (57%)
- Academic (22%)
- Consultant (14%)
- Regulatory (7%)
Relationships between Facilitators and Barriers to Harmonization

1. Healthy stakeholder relationships
   - Communication (e.g., dialogue, information sharing)
   - Transparency
   - Understanding

2. Well intentions
   - Trust
   - Willingness

GOALS
1. Economies of scale in evidentiary data; and/or
2. Harmonizing Process/Logistic aspect

3. Clearly defined governance and leadership
   - Legal
   - Financial
   - Feasibility

4. Available organizational infrastructure
For more details on this project:

- Today: Concurrent session B5

Lisa Masucci, Bernice Tsoi, Kaitryn Campbell, Daria O’Reilly, Mike Drummond, Ron Goeree. *Harmonization and Alignment of HTA Reimbursement and Regulatory Processes for Non-pharmaceutical Health Technologies*
Interactions between HTA/Coverage and Regulatory Processes

Selected points from a discussion in the HTAi Policy Forum in January 2011

Chris Henshall
Chair, HTAi Policy Forum
Honorary Fellow, Centre for Health Economics, University of York, UK
Content of Presentation

• HTAi Policy Forum
• Aims of Forum meeting on HTA and Regulation
• Stakeholder perspectives
• The Forum’s views on
  – Goals
  – Principles
  – Challenges
  – Opportunities
HTAi Policy Forum

• Provides opportunity for senior people from public and private sector organizations with strategic interests in HTA to discuss present state of HTA, its development and its implications for health care systems, industry, patients and other stakeholders.

• Membership is by application. Current membership 28 organisations.

• One main (48 hour) meeting per year
  – Forum chooses topic of current importance
  – Background paper prepared
  – Agenda focuses on plenary and group discussion with short presentations to define issue and facilitate discussion
  – Chatham House Rule

• Paper published in IJTAHC
Aims of meeting on HTA and Regulation

There is increasing interest in interactions between HTA, coverage and regulatory processes and bodies. The Forum meeting aimed to identify:

- **Goals of improved interactions** – what’s driving all this and what are we trying to achieve?
- **Principles that should underlie interactions** – how should we go about it?
- **Challenges** – what’s going to get in the way and how can we address these challenges?
- **Opportunities** – what can we do – in the short and longer term - to achieve the goals of improved interactions
Stakeholder perspectives

• **Patients** – want new treatments; and rapid access to beneficial products

• **Clinicians** – want new treatments; information on the real-world effectiveness and risks of products; and freedom to offer patients what they believe is best for them

• **Governments and health care providers** – wish to protect their population from harmful products and ensure they have access to products that address important health needs; wish to ensure that healthcare system(s) meet health needs of the population and offer value for money; promote success of healthcare industry R&D and/or manufacturing based in their country; and minimize budget impact
Stakeholder perspectives (2)

• **The general public** (whether or not patients) – expects rapid access to improved new products while being protected from harm; tends to look for certainty and expects official bodies and healthcare systems to provide it and to be accountable, transparent, consistent, and efficient

• **Industry** – wants to develop and market safe, effective, and profitable products; wants clarity and predictability in evidence requirements from regulators and coverage bodies over the product life cycle, and convergence of requirements where that is possible; cautions that without some progress in these areas, new product development will be increasingly difficult and costly
Improving Interactions: Goals

- **Speed patient access to valuable products**
- **Remove unnecessary barriers to successful development and appropriate market access for innovative products**
- Give manufacturers greater clarity about what evidence is required by which bodies and when
- Improve alignment of the timing and logistics of processes where appropriate
- Align methodological guidance and data requirements for establishing safety, efficacy, effectiveness, and comparative efficacy and effectiveness in so far as necessary and possible, and to be clear why requirements differ when they do
- Give patients and the public better understanding of the reasons for decisions by regulators and coverage bodies, especially where these differ
Improving interactions: principles

• Regulatory, HTA and coverage bodies should work together where possible and appropriate to maximize benefits for patients and the public

• Patients, industry and clinicians need to be actively engaged in discussions about regulatory, HTA and coverage processes; the wider public perspective also needs to be considered

• All parties and stakeholders need to be clear and open about their remits, goals and interests
Improving interactions: principles (2)

• All parties need to accept that, while improvements in coordination should be sought, the missions of regulators and coverage bodies are different and some evidence requirements differ accordingly

➢ There are legitimate (e.g., based on statute) occasions when a product granted regulatory approval will not be covered in a particular health care system for some or all of its licensed indications
Improving interactions: potential challenges

• **Lack of trust and understanding**
  - insufficient understanding within regulatory, HTA, and coverage bodies, industry and other stakeholders of each other’s purposes, remits, and processes; this can lead to lack of trust and unrealistic expectations about the extent of coordination and agreement that can be achieved

• **Organizational goals and culture**
  - The goals and priorities of regulatory, HTA, and coverage bodies are different and they have different traditions, ways of working, and relations with stakeholders.
Improving interactions: potential challenges (2)

• **Stakeholder involvement**
  – There is a need to involve clinicians and patients in discussions about the relationship between regulatory, HTA, and coverage processes.

• **Information issues**
  – There is concern in HTA and coverage bodies that industry may not disclose to them all relevant information about a product, while industry has concerns about the security of proprietary information if shared with HTA and coverage bodies. Legal constraints may limit information sharing between regulatory and other bodies.
Improving interactions: opportunities for progress

• Continue dialogue to promote interaction, understanding and trust

• Align scientific advice on design of pre- and post-market evaluations (see next two slides)

• Extend dialogue to address unmet needs
  ➢ Initiate discussions among manufacturers, public health and health system leaders, and regulatory and coverage bodies, on unmet needs and the development, assessment and coverage of products to address them
Align scientific advice on design of pre- and post-market evaluations (1)

1. Build on current work to develop **joint scientific advice** from regulatory/HTA/coverage bodies **for individual manufacturers** on the design of pre-market evaluations (e.g., phase II/III trials) for **specific products**, expanding to more products, more jurisdictions, and to phase IV study design.

2. Develop **joint scientific advice** from regulatory/HTA/coverage bodies **for the industry** on the design of pre- and post-market evaluations (e.g., phase II/III/IV studies) for **specific conditions**, including such matters as appropriate comparators, outcome measures, study populations and subgroups.

- **These might be initiated in a particular region of the world, with the ultimate aim of developing internationally recognized guidance (allowing for the regional variations on specific issues) if possible.**
Align scientific advice on design of pre- and post-market evaluations (2)

3. Develop joint scientific advice from regulatory/HTA/coverage bodies for the industry on the general design of pre- and post-marketing evaluations to maximize their value to regulators, coverage bodies, clinicians and patients; eg:

- inclusion criteria
- subgroups
- patient cross-overs in trials
- general principles underlying choice of comparator
- primary and secondary endpoints, surrogate and patient/clinically relevant outcome measures, QoL measures
- relating trial populations to wider populations (e.g., to enhance power of phase IV population studies)

4. Promote active engagement of industry, patients and clinicians in all of these developments
Possibilities for Harmonizing Regulatory and HTA Processes and Evidence Requirements: Regulatory Perspective

Barbara J Sabourin
Director General, Therapeutic Products Directorate, HPFB, Health Canada
CADTH Symposium 2013
Assessment process:
What information is considered?

Information provided by the sponsor (ICH, eCTD):
- **Efficacy**: “substantial evidence of the clinical effectiveness of the new drug for the purpose and under the conditions of use recommended”
  - Pivotal clinical studies
  - Possibly also “supportive” clinical studies
  - Phase I data
- **Safety**: “detailed reports of the tests made to establish the safety of the new drug for the purpose and under the conditions of use recommended”
  - All relevant clinical studies when at least one dose of study drug administered
  - All relevant non-clinical data
  - Phase I data
  - Post-marketing data if available

Information outside the submitted dossier (eg. Expert advice, medical literature, treatment guidelines, info from other regulatory bodies)
Possible Types of New Drug Submission:

- Standard NDS for a New Active Substance
- Priority NDS:
  - serious, life-threatening or severely debilitating disease or condition for which there is substantial evidence of clinical effectiveness that the drug provides effective treatment or significant benefit
- NOC with conditions:
  - may be granted for a drug with promising clinical benefit
  - creates mechanisms for the appropriate completion of confirmatory trials to verify the clinical benefit
  - “letter of undertaking” and follow-up of conditions
Trial Design Considerations:

- Canada follows ICH E10 “Choice of Control Group in Clinical Trials”
  - Describes general principles, including scientific and ethical considerations
  - Includes flow chart of basic logic for choosing control group
- All trials involve risk to participants
  - Their rights, safety and well-being need to be upheld under the conditions of the trial
  - The trial needs to be scientifically sound
Some Scenarios for Drug Approval:

• No existing standard treatment
• Effective standard treatment exists, experimental therapy expected to replace it
• Effective standard therapies exist, experimental therapy would be one more option
• Standard therapies exist as combination treatment, experimental therapy would be added on (adjunctive therapy)

There are several other possibilities.
Example: Kalydeco™ (ivacaftor)

- **Indication:** treatment of cystic fibrosis (CF) in patients age 6 years and older who have a G551D mutation in the CFTR gene
- **Trials:** two pivotal Phase III placebo-controlled studies in patients with CF who have a G551D mutation in the CFTR gene.
  - Phase II clinical study showed a lack of efficacy in patients with two copies of the most frequent mutation, F508del.

From Summary Basis of Decision (Priority Review)
Example: Crestor (Rosuvastatin calcium)

- **Indication:** hypercholesterolemia; prevention of major cardiovascular events
- **Trials:**
  - to support hypercholesterolemia claim: dose-ranging, <20 patients per arm, placebo controlled
  - Trials to support prevention of major cardiovascular events claim: JUPITER trial (from PM) double blind, placebo controlled
  - >89000 screened, >17000 randomized

From Product Monograph
Example: Dificid (fidaxomicin)

- **Indication:** indicated in adults (≥18 years of age) for the treatment of *Clostridium difficile* infection (CDI).
- **Trials:** two multicentre, double-blind, randomized, parallel group Phase III studies, where a non-inferiority design was used to compare the safety and efficacy of 400 mg/day Dificid (200 mg every 12 hours) with 500 mg/day vancomycin (125 mg every 6 hours) for 10 days in patients with confirmed CDI, (diarrhoea and presence of either toxin A or toxin B of *C. difficile* in the stool).
Key Documents in Regulatory Decisions:

• Review Reports
  • Quality; Clinical; Labelling
  • Manager’s memo

• Executive Summary

• Authorization package:
  ✓ Product Monograph
  ✓ Authorization document

✓ Summary Basis of Decision
  • Rationale supporting authorization
  • Only for subset of decisions
  ✓ Means publicly available
Current Regulatory Challenges

- Current analysis process not standardized, both on the part of regulators and sponsors
  - Review outcomes not always consistent with other regulatory agencies even when looking at same data package

- Develop qualitative or semi-quantitative framework for B/R assessment of medicines (under development)

- Regulatory authorization and HTA recommendations differ
  - Share information on basis for decisions, understand both sets of requirements
  - Increased collaboration between CADTH and HPFB / TPD
Interaction between CADTH and TPD

Interactions with Industry
- Pre-submission meetings
- Pipeline meetings
- Product Monograph Finalization Meetings

Scientific Advisory Committee Meetings

Drug Safety and Effectiveness Network
CADTH Annual Symposium
Explanatory or Exploratory Meetings
Concluding Comments

- Evaluation processes and practices continue to evolve for regulators and HTA communities
- The goal:
  - Evidence based decisions
  - Transparency and cooperation among partners
  - Lack of duplication
- The result: safe, effective high quality pharmaceuticals

Thank you!
Barbara.j.sabourin@hc-sc.gc.ca
Harmonization and Alignment of Regulatory and Reimbursement Evidence Requirements
Experience Gained To Date

Michael Drummond
Centre for Health Economics,
University of York
Outline of Presentation

• What we found in our study
  - alignment of evidentiary requirements
  - early tripartite dialogue
  - parallel submission
  - adaptive licensing

• Main insights/challenges
Alignment of Evidentiary Requirements

- Most focus has been on changes to accommodate the needs of payers
- Common areas of alignment include:
  - choice of comparator
  - choice of outcome(s) (eg intermediate or final)
  - length (eg time horizon) of studies
  - orientation of studies (eg effectiveness versus efficacy)

- Regulators not keen to compromise the key elements of study design, but there is a genuine interest in producing data of more relevance to clinicians and payers
- Alignment should include considerations of evidence post-launch as well as pre-launch
## Existing Early Tripartite Dialogue Processes

<table>
<thead>
<tr>
<th>Region/Country</th>
<th>Stakeholders (i.e. assessment agencies)</th>
<th>Name of Program</th>
<th>Type of activities</th>
<th>Type of technology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australia</td>
<td>TGA (Regulator)</td>
<td>N/A (pilot programme)</td>
<td>Scientific advice: -Product specific</td>
<td>Pharmaceuticals</td>
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<td>PBS (Coverage body)</td>
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<tr>
<td>Canada</td>
<td>HC (Regulator)</td>
<td>Joint pipeline meetings</td>
<td>Scientific advice: -Product specific</td>
<td>Pharmaceuticals</td>
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<td>CADTH (Coverage body)</td>
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<tr>
<td>England</td>
<td>MHRA/EMA (Regulator)</td>
<td>NICE Scientific Advice Programme</td>
<td>Scientific advice: -Product specific</td>
<td>Pharmaceuticals</td>
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<td></td>
<td>NICE (Coverage body)</td>
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<td>Intent to expand to non-pharmaceuticals</td>
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<tr>
<td>Sweden</td>
<td>MPA (Regulator)</td>
<td>Joint Scientific Advice Meetings</td>
<td>Scientific advice: -Product specific</td>
<td>Pharmaceuticals</td>
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<td>TLV (Coverage body)</td>
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<tr>
<td>Europe</td>
<td>EMA (Regulator)</td>
<td>EMA Road Map to 2015</td>
<td>Scientific advice: -Product specific, -Disease-specific</td>
<td>Pharmaceuticals</td>
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<td></td>
<td>EUNetHTA (Multi-national HTA network)</td>
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<tr>
<td>Europe</td>
<td>Multiple stakeholders, including:</td>
<td>Tapestry Network</td>
<td>Scientific advice: -Product-specific, -Disease-specific</td>
<td>Pharmaceuticals and diagnostic devices</td>
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<tr>
<td></td>
<td>EMA, MHRA, MPA, BfArM, AFSSAPS, AIFA. (Regulators)</td>
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<td>NICE, TLV, G-BA, CEPS, AIFA (Coverage bodies)</td>
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<td>EUNetHTA (as observer)</td>
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<td></td>
<td>FDA (as liaison)</td>
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<tr>
<td>Global</td>
<td>Multiple HTA stakeholders</td>
<td>Green Park Collaborative</td>
<td>Scientific advice: -Disease-specific, -General</td>
<td>Pharmaceuticals</td>
</tr>
</tbody>
</table>

Italian Medicines Agency (AIFA); French Health Products Safety Agency (AFSSAPS); Federal Institute for Drugs and Medicines (BfArM); Canadian Agency for Drugs and Technologies in Health (CADTH); Economic committee on health care products (CEPS); European Medicines Agency (EMA); European Network for Health Technology Assessment (EUNetHTA); Food and Drugs Administration (FDA); Health Canada (HC); Federal Joint Committee (G-BA); Medicines Product Agency (MPA); Medicines and Health care products Regulatory Agency (MHRA); National Institute for Health and Clinical Excellence (NICE); Pharmaceutical Benefit Scheme (PBS); Therapeutic Goods Administration (TGA); Dental and Health Benefits Agency (TLV)
Early Tripartite Dialogue

• Useful for improving the level of understanding and trust between the various parties
• Timing of the dialogue is important (e.g. before the major clinical studies begin)
• Possible level of prescription in the advice might vary by disease area (more experience needs to be accumulated on this)
• Important to involve all the major stakeholders in a given jurisdiction (e.g. national, provincial, hospital)
• Advice is considered more valuable if it is likely to be stable through time
## Existing Parallel Submission Activities

<table>
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<tr>
<th>Region/ Country</th>
<th>Stakeholders</th>
<th>Name of Program</th>
<th>Type of Technology</th>
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</thead>
</table>
| **Australia (2011)** | TGA (Regulator)  
PBAC (Decision maker) | Parallel TGA and PBAC processes | Pharmaceutical |
| **Canada (2009)** | Health Canada (Regulator)  
CADTH (HTA) | CADTH Pre-NOC Priority Review | Pharmaceutical |
| **Canada (2012)** | Health Canada (Regulator)  
OHTAC (Decision maker) | MaRS Excellence in Clinical Innovation and Technology Evaluation (EXCITE) | Non-pharmaceutical |
| **USA (2010)** | FDA (Regulator)  
CMS (Coverage body) | FDA and CMS Memorandum of Understanding | Non-pharmaceutical |

Canadian Agency for Drugs and Technology in Health (CADTH); Centers for Medicare & Medicaid Services (CMS); FDA (Food and Drugs Administration); Ontario Health Technology Advisory Committee (OHTAC); Pharmaceutical Benefits Advisory Committee (PBAC); Therapeutic Goods Administration (TGA)
Parallel Submission

- Major potential benefits in reducing the time between regulatory and reimbursement decisions
- Possible risk of wasted effort (in HTA) if the product eventually fails to gain regulatory approval
# In-practice or Pilots of Adaptive Licensing

<table>
<thead>
<tr>
<th>Country/Jurisdiction (Year Introduced)</th>
<th>Agencies involved</th>
<th>Name of program</th>
<th>Technology</th>
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<tbody>
<tr>
<td><strong>Europe</strong></td>
<td>EMA (Regulator) EUNetHTA and other HTA organization (HTA) Patient representatives Payers Licensing Authorities Drug Developers</td>
<td>Road Map to 2015</td>
<td>Pharmaceuticals</td>
</tr>
<tr>
<td><strong>Canada (2007)</strong></td>
<td>Health Canada (Regulators)</td>
<td>Health Canada Progressive Licensing Project</td>
<td>Pharmaceuticals Biologics</td>
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<tr>
<td><strong>USA (2009)</strong></td>
<td>Singapore Health Authorities (Regulator) Payers Drug developers Healthcare professionals Academics Patient-advocacy groups</td>
<td>MIT New Drug Development Paradigms (NEWDIGS)</td>
<td>Pharmaceuticals</td>
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<tr>
<td><strong>Singapore (2011)</strong></td>
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*European medicine authority (EMA); European Network for Health Technology Assessment (EUnetHTA)*
Adaptive Licensing

• Aims to improve the quality and timeliness of knowledge development, whilst providing more tightly managed market entry
• Can take many forms and goes under several names
• Concept can be extended to incorporate ‘coverage with evidence development’
• May be particularly suitable for non-pharmacological technologies
General Challenges

• Maintaining trust and avoiding ‘turf’ disputes

• Determining the extent of confidentiality (e.g., separating product-specific issues from general ones)

• Recognizing that these approaches can be resource-intensive and mobilizing resources accordingly