Operational Considerations for Running Effective Expanded Access Programs: Spotlight on Oncology

Rebecca Thompson
Jean-Louis Merot, MD
March 25, 2014
Polling Questions

- A small number of polling questions have been added to today’s webinar to make the session more interactive.
Your Presenters

**Rebecca Thompson**  
Client Engagement Manager, Health Engagement & Communications, Quintiles

Rebecca Thompson has over 7 years experience managing late-phase clinical studies, including expanded access programs, safety studies, device studies and observational studies. With extensive global experience, she has conducted a number of large programs in a variety of indications, including oncology, respiratory, neurology, obesity, chronic pain, cardiovascular, endocrine, diabetes, and infectious disease. She is currently serving as a Manager, Quintiles Health Engagement & Communications, and prior to this role she managed Phase III, IIIb and IV clinical trials for over 6 years in the Real-World & Late Phase Research Group at Quintiles. She has led the successful execution of 6 Expanded Access Programs including 2 global oncology programs spanning 28 countries. She earned her B.S. in Biology and Chemistry at the University of North Carolina at Chapel Hill and started her career in clinical research at the University of North Carolina Center for AIDS Research, working on HIV/AIDS expanded access programs.

**Jean-Louis Merot, MD**  
Senior Medical Management Director, Oncology Medical Advisor Unit, Quintiles

Dr. Merot graduated from Rennes University in France with additional qualification in clinical research methodology and statistics. He has an M.B.A. in Pharmaceutical Industry from the Tours Business School in France. Dr. Merot’s career in clinical research started with Syntex Laboratories in 1990 as a clinical research physician. In 1993, he joined Benefit International; a CRO specialized in pharmacoconomics and quality of life, where he held a project management and consulting role for six years. Dr. Merot has managed clinical trials for 23 years, primarily in the late phase area. His experience with Quintiles over the last 20 years includes both interventional and observational international studies in various indications, including oncology. In his current role, he provides senior medical oversight within the oncology medical advisor team at Quintiles.
Agenda

• What is an EAP? Why would you run an EAP?
• What are the regulatory concerns or implications?
• Operational considerations, challenges and expertise needed when designing an EAP
• EAPs for oncology products
• Case studies
• Q&A
Today’s Webinar Audience

- Academia: 45%
- Biostatistician: 1%
- Clinical Operations: 27%
- Epidemiology: 2%
- Health Economics/Health Outcomes: 3%
- Medical Affairs: 8%
- Medical Affairs: 1%
- Medical Affairs: 1%
- Medical Affairs: 11%
- Medical Affairs: 1%
- Risk Management: 1%
- Other: 1.0%
What is an EAP?
Rebecca Thompson
Polling Question

What is your experience in running EAPs?

> None
> 1-2
> 3-5
> More than 5
What is an Expanded Access Program?

• An Expanded Access Program (EAP) is a program that provides access to investigational products to treat patients with serious or immediately life-threatening conditions who have no satisfactory alternative treatment options.

• Also known as “compassionate use” programs (CUPs) and early access programs.

• The investigational products have not yet been approved by regulatory authorities.

• Typical indications include Oncology and Infectious Disease (HIV/AIDS, Hepatitis)

• Typically completed as a Phase IIIb study
EAP Guidance – FDA¹

• Published Final Rules in August 2009 on:
  > Expanded Access to Investigational Drugs for Treatment Use
  > Charging for Investigational Drugs

• Regulations address 3 types of EAPs:
  > Individual patient or emergency use
  > Intermediate-Size (approx 10-100 subjects)
  > Large groups under a treatment protocol or treatment IND

• Notes that EAPs may also refer to use of an approved drug, where availability is limited by a risk evaluation and mitigation strategy (REMS), for diagnostic, monitoring, or treatment purposes, by patients who cannot obtain the drug through the REMS.

¹Food and Drug Administration (US):
EAP Guidance – EMA²

• EAPs are typically referred to as Compassionate use programs (CUPs).

• Governed by legislation in individual EU Member States

• Member States can ask the European Medicines Agency’s Committee for Medicinal Products for Human Use (CHMP) to provide an opinion

• Article 83 of Regulation (EC) No 726/2004 published in March 2004 by the CHMP is complimentary to MS legislation and provides an opinion on conditions for CUPs. The aim of Article 83 is to:
  > Improve access to CUPs in the EU Member States
  > Promote a common approach to CUP implementation
  > Increase transparency between member states in terms of treatment availability

EAP Limitations

• The primary objective is to provide early access to treatment. EAPs do not have a research rationale and data collection is often limited to safety data.

• Consideration must be given to avoid conflict as an EAP may be perceived as a “seeding” study or in conflict with the Anti-kickback Statute in the US specifically.

• Enrollment cannot compete with enrollment into ongoing clinical trials
Why run an Expanded Access Program?

• Primary object is to provide patients early access to potentially life-improving or saving treatments prior to regulatory approval

• May serve as a way to provide patients continued access to treatment following a pivotal trial

• Expand availability of the investigational product beyond the patient population typically seen in a Phase II or III study

• Provide pharmaceutical companies a way to collect additional safety data and expand the safety profile of the therapy

• Provide pharmaceutical companies a way to gain pre-market experience and establish a base of patients that may continue to utilize the investigational product upon approval
Most Common Designs for EAPs

1. **Clinical Trial Design**— protocol-driven and completed under a treatment IND (US - for large patient populations) or pending application for marketing authorization (EU/ROW).
   - Mimics clinical trial standards (i.e. Inclusion/Exclusion compliance, safety reporting, etc.)

Clinical Trial Design

- Primary purpose is access to therapy
- Sample size may be limited by sponsor
- Protocol filed under treatment IND (US)
- Ethics/IRB approval required. Access may not begin until 30 days after FDA received protocol (US)
- Data collection permitted
- Protocol defines the inclusion/exclusion criteria
- Study monitoring – established by sponsor and may include hybrid or central monitoring only
- Adverse Events/SAEs reported to Sponsor and Sponsor reports to regulatory agency per guidelines for a clinical trial.
Named Patient (EU) / Individual Patient (US) Design

- Regulatory approval requested on a case-by-case basis and typically done by the physician
- Does not typically involve a protocol
- Ethics/IRB approval required (in emergency situations approval/notification is done post treatment)
- Limited safety data collected and virtually no other data collected
- Safety information reported directly to the regulatory agency
- Can be very labor intensive for the physician(s) involved
## EAPs vs. Typical Registrational Trials

<table>
<thead>
<tr>
<th>Item</th>
<th>Typical Registrational Trial</th>
<th>Expanded Access Program</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Research Purpose</strong></td>
<td>• Data collected to support safety and efficacy, dosing, etc. in order to gain market approval</td>
<td>• Early access to therapy with minimal safety data collected</td>
</tr>
</tbody>
</table>
| **Regulatory Approvals** | • Uniform protocol and study design globally  
• Protocol and IRB/Ethics approval required | • May use multiple design approaches in various countries  
• Protocol and IRB/Ethics approval typically required |
| **Timeline**       | • Defined timeline for start-up through close-out                                           | • Depending on design, timeline for start-up may be "just-in-time" to accommodate emergency treatment needs.  
• Close-out timelines are typically dependent on regulatory approvals and/or commercial availability |
## EAPs vs. Typical Registrational Trials (continued)

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<th>Item</th>
<th>Typical Registrational Trial</th>
<th>Expanded Access Program</th>
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<tr>
<td><strong>Site Selection</strong></td>
<td>• Various methods available for site selection that can be determined by the Sponsor. • Typically includes a specified review process for selecting qualified sites.</td>
<td>• Site selection is not generally driven by conventional criteria • Site may “self select” and may have little to no prior research experience • Sites may also be selected as a result of subject self referral</td>
</tr>
<tr>
<td><strong>Patient Enrollment</strong></td>
<td>• Defined enrollment goals at the start of the study typically including a limit for the analysis. • Often include advertising/outreach to recruit patients</td>
<td>• May have an expectation based on demand and drug availability but enrollment normally continues until regulatory approval is received. • Sponsor or Advisory Board may provide limits on treatment (i.e. number of sites/subjects) • No advertising for patients or recruitment incentives for sites.</td>
</tr>
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</table>
## EAPs vs. Typical Registrational Trials (continued)

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<th>Item</th>
<th>Typical Registrational Trial</th>
<th>Expanded Access Program</th>
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<tbody>
<tr>
<td>Data Collection</td>
<td>• No limitations on what data can be collected (i.e. efficacy, safety) and how (i.e. paper vs. eCRF)</td>
<td>• Limited to safety data and is dependent on local country regulations</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• CRF size and the number of data points should be as minimal as possible</td>
</tr>
<tr>
<td>Site Payments</td>
<td>• Typical budgets include start up payments, payments for subject visits, pharmacy fees, etc.</td>
<td>• Typically includes no/minimal compensation</td>
</tr>
<tr>
<td>End of Study</td>
<td>• Study closed based on pre-defined timeline following last subject off treatment</td>
<td>• Patients migrated to commercial product upon availability</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Specific transition plans must be established prior to commercial availability and the processes will differ based on local regulations</td>
</tr>
</tbody>
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Polling Question

- Does your organization plan to run an EAP in the next two years?
  - Yes
  - No
  - I don’t know
EAP for Oncology Products
Jean-Louis Merot, MD
EAP for Oncology products

- Why oncology focus for EAPs
- Current situation and trends
- Risk and benefits of EAPs in the Oncology Area
- Examples of EAP in the Oncology Area
Why oncology Focus for EAPs

- Epidemiology & Marketing reasons
- Regulatory acceptance of EAPs
- Patient pressure
- Life threatening conditions
- Unmet medical needs
- Targeted Therapies
Why oncology Focus for EAPs

Regulatory Acceptance

• Recent article* analysing Trials supporting by FDA approval between 2005-2012
• Cancer indications revealed special features:

1. Results show flexibility in terms of alternative study designs for Cancer drug approvals
2. EAPs not Designed to be Pivotal Efficacy trials but can become essential to approval
3. Support potential role EAPs may have in oncology drugs approvals

*Clinical trial Evidence supporting FDA approval of Novel Therapeutic Agents, 2005 -2012.
Downing N.S & al.JAMA, 2014; (311(4):368-377
Current situation & trends

- Search of EAPs registered on ICTRP database* since 1999
- Using Key words: “Compassionate use “ or “EAP” or “Expanded access”

EAP studies
Oncology vs Non Oncology

Number of oncology EAPs stable since 2005

Is the 2010-2013 drop in % a trend or an artifact?

*http://apps.who.int/trialsearch/
Current situation & trends

- Search of EAPs publications on “www.PubMed.gov”

Oncology Vs Non oncology EAPs publication

Oncology EAPs not growing as fast as non oncology indications

WHY?
Current situation & trends

Potential Reasons for fewer oncology EAPs

<table>
<thead>
<tr>
<th>More New drugs in Oncology</th>
<th>Importance of clinical trials in Oncology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sponsor related reasons</td>
<td>CT site Registration</td>
</tr>
</tbody>
</table>
Polling Question

- Do you have a set strategy regarding Clinical Trial Website registration and publication when undertaking an EAP in Oncology?
  > CT website registration only
  > Publication only
  > Both CT website registration & publication
  > None
  > Variable from 1 EAP to another
PRO and CONs of EAP in Oncology

**PROS**
- Adds alternative to patients
- Increases drug access to patients
- Can help new indication dvpt
- Contributes to get safety data earlier
- May support regulatory approval

**CONS**
- Increases physician workload
- Risk of unknown safety profile
- Risk to CT recruitment
- Cost to Sponsor
EAP in Oncology

Conditions for EAP participation

- Life threatening condition
- No acceptable Treatment alternative
- Patient not eligible for a clinical trial
- Large scale or intermediate Scale program offered by manufacturer?
  - If yes = « cohort « EAP
  - If no = single patient program
Access to Treatment

• Despite massive research investment, there continue to be many areas of unmet medical need in oncology:
  > Many cancer patients face the situation where no curative treatment option is available.
  > Patients for whom phase II or III oncology treatments have been successful, may be given the option to stay on treatment until the product is made commercially available.

• This is made possible through Expanded access / compassionate use programs.
# Oncology EAPs examples

<table>
<thead>
<tr>
<th></th>
<th>STUDY 1</th>
<th>STUDY 2</th>
<th>STUDY 3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Objective</strong></td>
<td>Provide treatment Evaluate safety profile</td>
<td>Provide treatment Evaluate safety profile</td>
<td>Provide treatment Evaluate safety profile</td>
</tr>
<tr>
<td><strong>Indication</strong></td>
<td>Refractory Breast cancer</td>
<td>Relapsing/ refactory Mantle Cell Lymphoma</td>
<td>Metastatic Gastric adenocarcinoma</td>
</tr>
<tr>
<td><strong>Design</strong></td>
<td>Open label, multicenter</td>
<td>Open label, multicenter</td>
<td>Open label, multicenter</td>
</tr>
<tr>
<td><strong>Endpoint</strong></td>
<td>Safety</td>
<td>Safety</td>
<td>Safety</td>
</tr>
<tr>
<td><strong>Sample Size</strong></td>
<td>No target sample size</td>
<td>Estimate. Not calculated</td>
<td>No target sample size</td>
</tr>
<tr>
<td><strong>Procedures/requirements</strong></td>
<td>Inv prior experience with product</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Study drug</strong></td>
<td>Provided until market availability</td>
<td>Provided until market availability</td>
<td>Provided until market availability</td>
</tr>
</tbody>
</table>
Study Overview

Aim

Establish broader safety evidence and fulfill an unmet medical need for patients with advanced cancer

Design

Interventional
Open-label, single arm study
3-4 year duration

Access  Safety

Patients & Sites

Approximately 1200 patients. Hospital sites.
Primary objective: safety and access
Secondary objective: efficacy and quality of life
## Operational Strategies for Success

A *real-world research mindset is critical to success*

### Challenge Solution Results

**Changing settings**
- Study size
- Study Teams
- Study Timelines
- Increased countries
- Medical affairs Vs Clinical Dvpt
- Tailored study timelines & budget
- Increased need for drug supply
- Staggered end of study

**Continuous Sponsor adaptations**

**High clinical demand**
- Increased risk of protocol deviations
- Lack of control on recruitment
- Protocol amendment
- Increased site workload
- Increased sample size

**Engaged Physicians**

**Change of study objective from EAP to pivotal regulatory study**
- Protocol amendment
- Project “relaunch”
- Increased snapshot analyses

**Enhanced product communication**
Conclusions

• But not so frequent
• Should be envisaged

EAPs in oncology

• Can support Drug approval
• Must not impede/compete CT

EAP & Oncology patients

• Increasing Public awareness
• All actors must be ready to answer

Oncology well suited for EAP
Upcoming Events

Real-World & Late Phase Research Webinars

Quintiles experts run regular webinars on Real-World & Late Phase Research services.

Topics include:

- DIABETES VALUE DEMONSTRATION
- ONCOLOGY VALUE DEMONSTRATION
- RARE DISEASE REGISTRIES
- EUROPEAN PHARMACOVIGILANCE LEGISLATION
- REGISTRIES 101
- MARKET ACCESS
- MAXIMIZING VALUE AND QUALITY IN PHASE IV

To register or view previous webinars please go to
www.quintiles.com/real-world-late-phase-webinars
Thank you

Questions?