



## ***Practical Guidance for Observational Research***

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# Agenda

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- How to get the most out of your study
- Who are the Key Stakeholders
- Do you really have an Observational Study?
- Overall Study Considerations
- Operational Aspects
  - Help Sites Perform Well
  - Patient Retention
- Data Collection
- Analyses
- More Info.....

# How To Get Most Out Of Your Study

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## Ensure you have agreement on:

- **Why** you are performing the study
  - Reimbursement?
  - Mandated study?
  - Marketing/ publication?
- **What** you are studying
  - Which patients or drugs are of interest
  - “Mandatory endpoints” or “usual care”: impact on design
  - Core protocol with or without local adaptations
  - “Nice to have” versus “need to have”
- **When** does the data need to be available
  - Deadline for abstracts are non-negotiable deadlines!
  - Global analyses, or local, or both

# Balancing the Various Stakeholders Involved in Observational Studies

## Internal

- Medical Affairs
- Medical
- Marketing
- Health Outcomes
- Data Management
- Sales
- Outsourcing



## External

- Physician/ Prescriber
- Regulatory Agencies
- Health Insurance
- Patients
- Media

**Now you have decided on why, what  
and when.....**

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**Is an observational study really  
what you have?**

# EU CT Directive – Non-interventional Clinical Trial = Observational Study



- ▶ “A study where the medicinal product(s) is (are) prescribed in the usual manner in accordance with the terms of the marketing authorization
- ▶ The assignment of the patient to a particular therapeutic strategy is not decided in advance by a trial protocol but falls within current practice
- ▶ ***The prescription of the medicine is clearly separated from the decision to include the patient in the study***
- ▶ ***No additional diagnostic or monitoring procedures are applied to the patients\****
- ▶ Epidemiological methods shall be used for the analysis of collected data”

*\*other than those which are ordinarily applied in the course of the particular therapeutic strategy in question.”*

# Observational vs Interventional

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- ▶ Interventional studies always need to go through Ethics review
  - ▶ Interventional design is possible without drug supply- this design could be performed with high patient numbers
  - ▶ If protocol drives drug treatment of patient, RA will want to review - this design has impact on patient numbers and budget
- ▶ Interventional-
  - ▶ Does not always impact timelines
  - ▶ Ethics often pleased to see scientific rationale increased
- ▶ Sometimes an interventional design can be the easier route!

# ....what if it is an observational study?.....

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Impact on the study

# Overall Study Considerations

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- Scientific Rationale needs to be clearly stated
  - Ethics Committees will review these carefully
- Protocol needs to be accepted by physicians
  - Needs to show benefit to the patient (can be for community as a whole)
  - Study needs to fit in their “usual practice” – even without protocol driven tests and visits, studies are a burden to investigators
- “Need to have” versus “nice to have” data
  - In order to have quality data, careful and early team discussions are needed
  - “Working backwards”

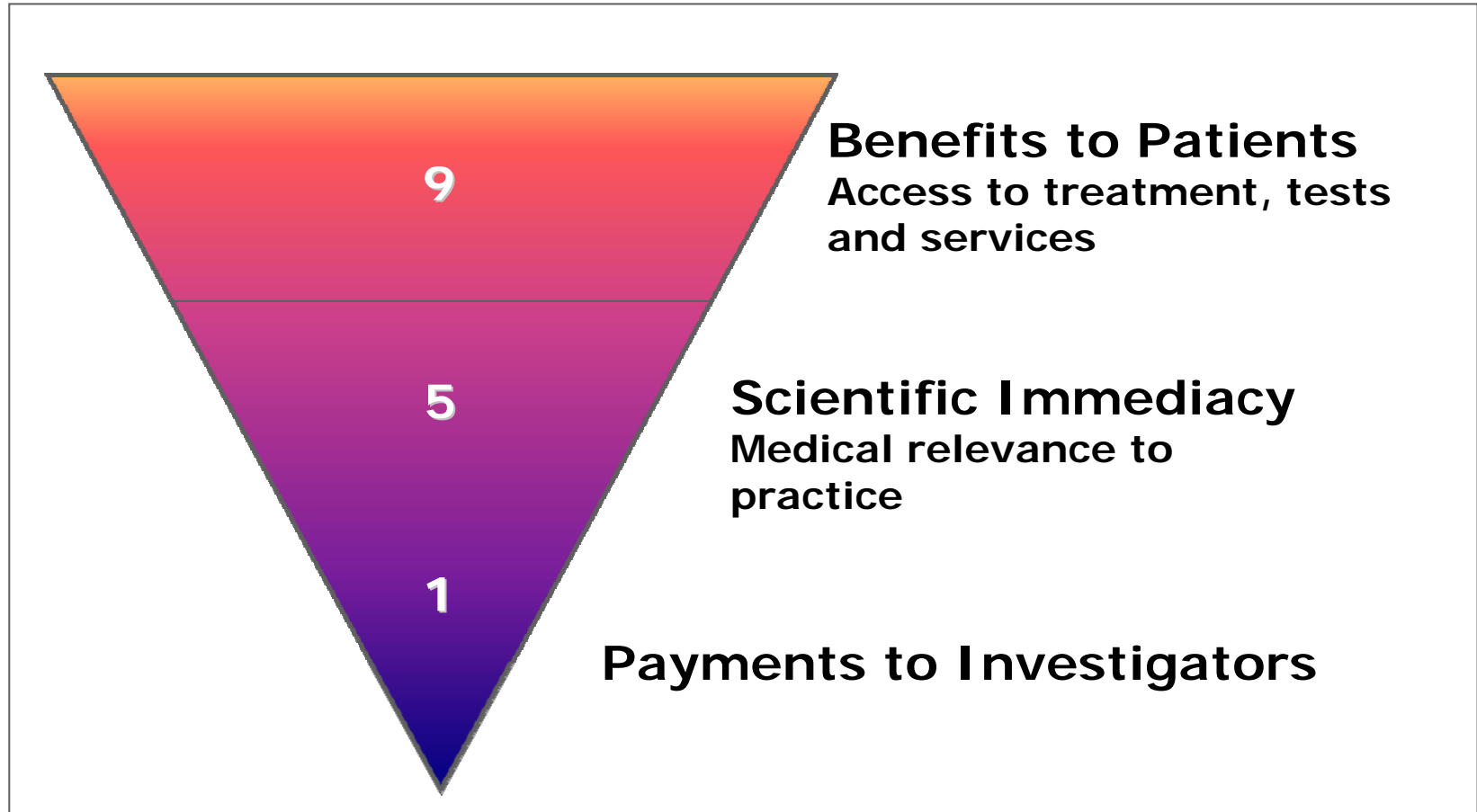
# Similarities & Differences

	Phase II/III	Observational Study
<b>Study Objectives/ Output</b>	NDA approval, efficacy and safety	Publication, market expansion, investigator experience, outcomes and safety
<b>Project Management</b>	Execute study, timelines, and budget	Execute study, timelines, budget, and market sensitive
<b>Study Start-up</b>	Investigator expertise, location, population	Larger investigator pool (naïve)- unknown territory, patient/investigator motivation
<b>Regulatory/Ethics</b>	Very organized and set rules	Differs from study to study, country to country and even region by region.
<b>Monitoring</b>	On-site, up to 100% SDV	Can vary from on-site to remote (ICH-GCP compliant); SDV on main critical data
<b>Data Management</b>	Wide range of tools	Complex and simple data capture tools including patient portal
<b>Analysis</b>	Post database lock	Any time during the study, endpoint analyses physician-collected and patient-reported endpoints

# Main Challenges in Observational Research

- Site ('s lack of clinical research) experience
- Data collected
  - Forms should be simple and small
  - “Need to know” versus “nice to know” data
- Monitoring
  - No need for 100% SDV – ICH/GCP require “ SDV appropriate to the design and use of data”
    - targeted monitoring should be considered- if at all
  - Emphasis on site management rather than monitoring
- Data Analyses
  - Ad hoc analyses need to be possible
  - More descriptive in nature- large patient numbers
  - Need to deal with missing data
  - But- SAP is needed

# Investigator Motivation Factors



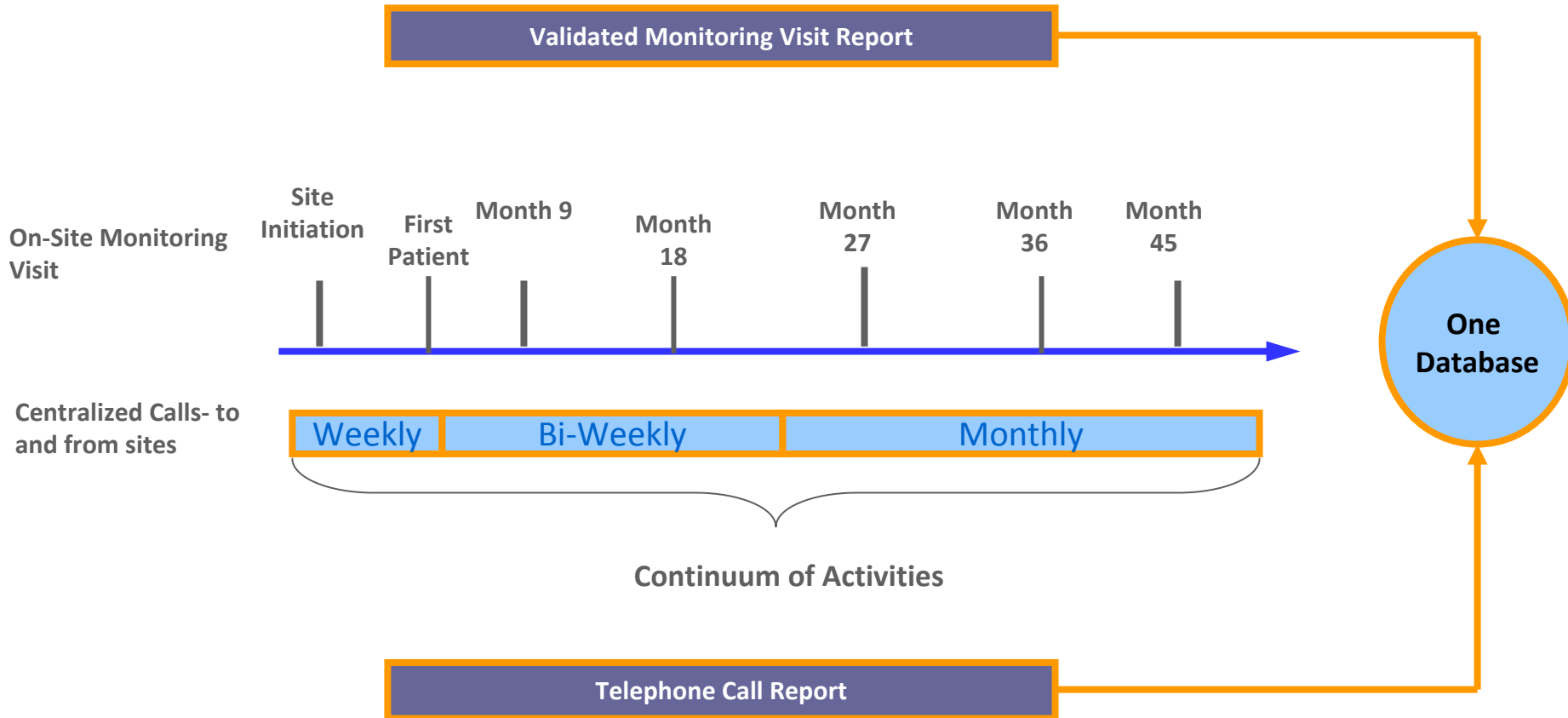
# Help Sites Perform Well !

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- Support services to decrease site burden
  - Training/education
  - Advertising and awareness campaigns
  - Patient retention support
- Best practice in feasibility analysis and site qualification
  - Validation of numbers of investigators and performance metrics
  - Feedback from previous studies/ teams and investigators
- Ability to offer a blend of on-site and centralized monitoring methods that are ICH/GCP compliant when study requirements allow
  - Results in cost/time efficiencies as well as decreased burden on study sites

# Hybrid Site Management and Monitoring

## Combination of calls and on-site visits



# **An Additional Important Consideration.....**

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**How to keep patients in the study**

# Patient Retention

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- A motivated site will have a higher retention of patients
- Investigator will need to maintain contact with patients from start to finish
- Investigator supported through outside party
  - Begins with ICF
    - Patient completes registration form at time of study consent
    - Own contact details plus Next of Kin
  - Regular confirmation calls are made to patient
    - If patient cannot be reached, NoK is contacted
    - Adhere to privacy laws
    - Caller will not have access to any medical details
- Minimizes lost to follow up and maximize endpoint capture
- If Lost of FU is biased- will impact analyses

## Data Collection....

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**Ensure Data Collection Tools fits  
purpose of study**

# Data Management Approach

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- Many technologies and techniques exist:
  - Paper CRFs
  - Facsimile or scanning systems
  - Electronic CRFs (EDC)
  - Direct patient data entry via PDAs or web-system (ePRO)
- Each approach has advantages and limitations
  - Each study must balance flexibility with data availability, data validity and cost
- Final system depends on many factors
  - Number of data elements
  - duration
  - follow-up frequency
  - number of sites
  - available resources
  - location

# ...and Finally....

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## Analyses

# Analyses

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- Analyses are not powered for differences, tend to be descriptive
- Strategies to deal with missing data and confounding are crucial
- Flexibility is key: Purpose of the analyses
  - Visibility of product
  - Abstract submissions
  - Production/Marketing decisions
  - Sharing data with investigators (motivation)
  - Stopping studies
  - ....and respond to market questions (if within research question)
- Therefore, DB needs to be ready for ad-hoc lock at any time
  - Ensure data cleaning plans incorporate this

# Study Reporting and Publications

- Clinical Study Report (CSR)
  - Some sponsors may require tables, listings and graphs only
  - Not necessarily ICH report but may be an abridged version, particularly if the study is for publication
  - Fewer detailed appendices
  - More communication-oriented, audience-conscious
  
- Publications
  - Often key deliverable of non-registration research studies
    - Peer-reviewed journals
    - Abstracts
    - Oral congress communication (podium presentations)
    - Sponsor internal communication

