Practical Elements of Trial Development: Regulatory Standards and Contracts

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If There is A Main Message …

Make sure you are working with pros!

Objectives

To review:

- Broad principles of randomized controlled trials
- Linking principles to regulations
- Linking principles to roles and responsibilities

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Broad Principles of Randomized Controlled Trials

If There is A Main Message …

- There are two extreme "attitudes" in conducting clinical trials: "Pragmatic" and "Explanatory"
- The trials have different objectives and are associated with results that have different uses
- Understanding where a the research question of a trial fits in this spectrum will help you understand many aspects of trial preparation, conduct and interpretation
- Consider the "continuum"

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Meyer RM. Contrasting Explanatory and Pragmatic Randomized Controlled Trials in Oncology. Education Book, American Society of Clinical Oncology 2011: 72-75.

“The Architecture of Clinical Research”

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Feinstein 1985

"The Architecture of Clinical Research"

RCTs have control and experiment groups that are assigned by random allocation

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Feinstein 1985

"The Architecture of Clinical Research"

RCTs have control and experiment groups that are assigned by random allocation

Two main things can go amiss: …

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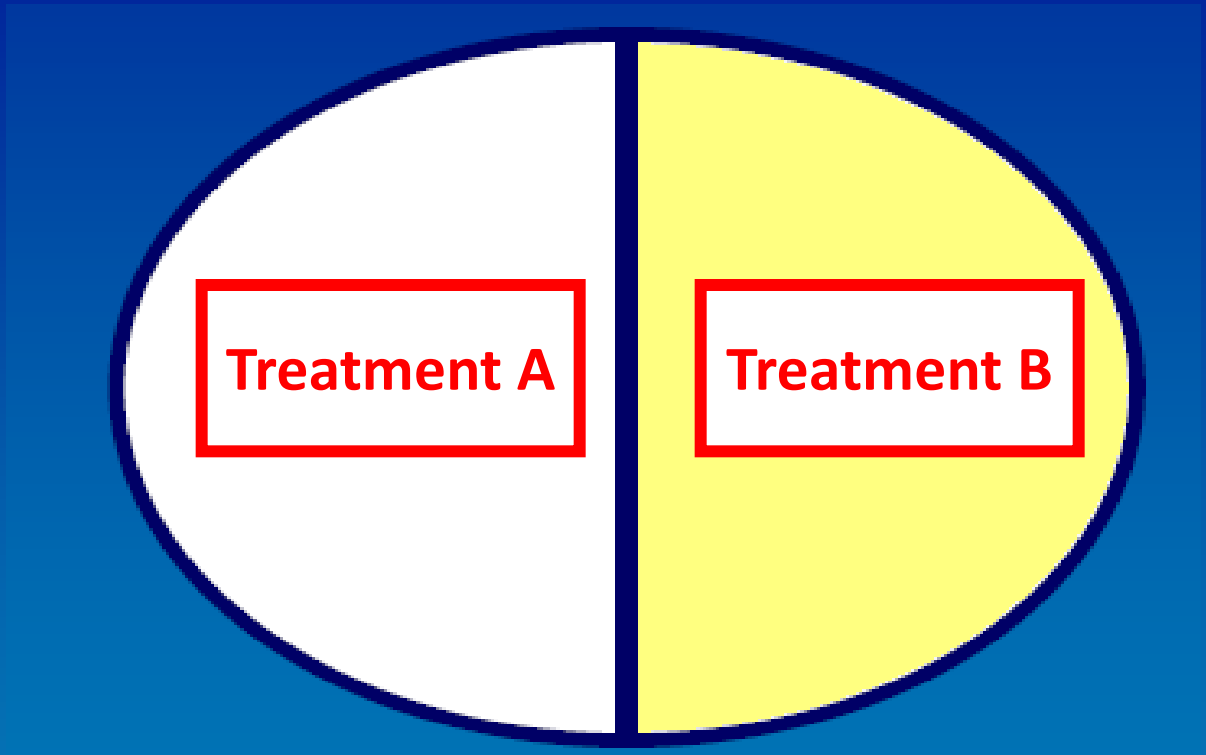
Feinstein 1985

Bias



Bias: Are these 2 populations similar?

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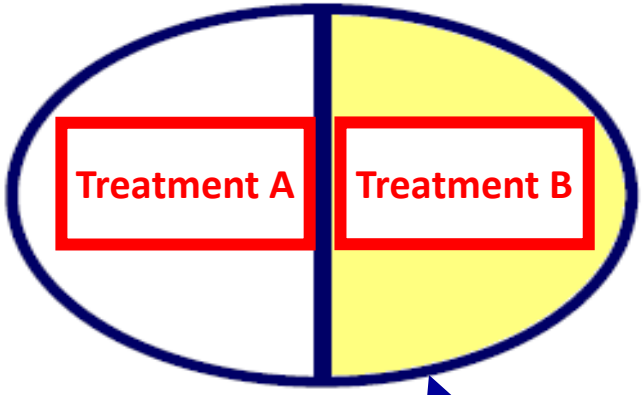
Feinstein 1985

Generalizability

Eventual Population of Interest



Study Population

Suitability: Does the study population represent the population of interest?

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Factors Influencing Bias and Generalizability

- How the cohorts are assembled
- How therapy is implemented
- What (and how) outcomes are assessed
- How data are analyzed

Factors Influencing Bias and Generalizability

- How the cohorts are assembled
- H
- V ed
- How data are analyzed

Trade-offs will exist:

Strategies to reduce bias may also reduce generalizability

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Explanatory vs. Pragmatic Trials

Explanatory

- Tests a biologic principle
- Emphasize efficacy

Pragmatic

- Tests a treatment policy
- Emphasize effectiveness

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Schwartz and Lellough, J Chron Dis, 1967

Example 1

The explanatory trial: Does 30 days of a radiosensitzer have a **biologic** benefit?

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Schwartz and Lellough, J Chron Dis, 1967

Example 2

The pragmatic trial: Does 30 days of a radiosensitzer have a **clinical** benefit?

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Schwartz and Lellough, J Chron Dis, 1967

Explanatory vs. Pragmatic Trials

Explanatory

- Tests a biologic principle

Today's trials do not have such extremes.

The methodologic differences are more subtle

- Tests a treatment policy
- Emphasize effectiveness

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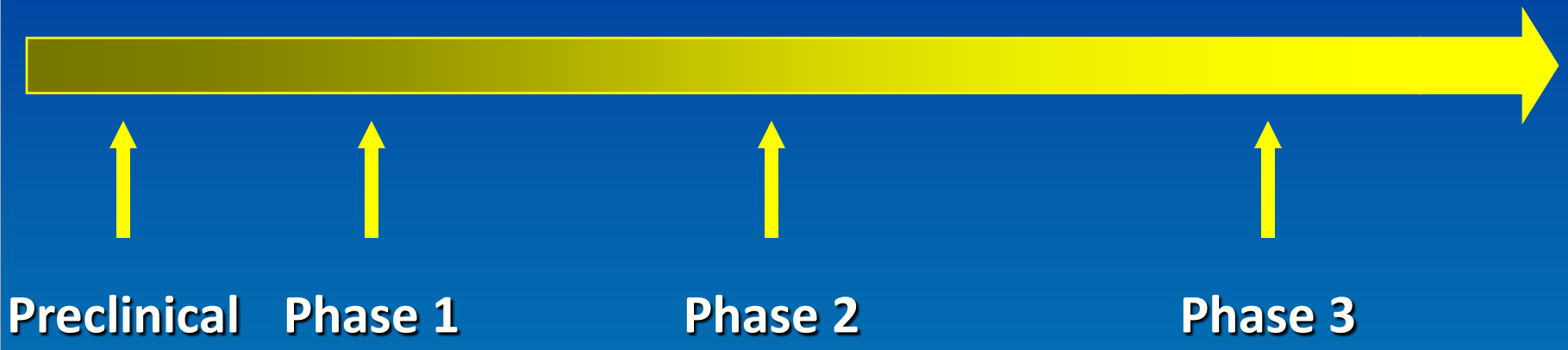
Schwartz and Lellough, J Chron Dis, 1967

Progression of Trials



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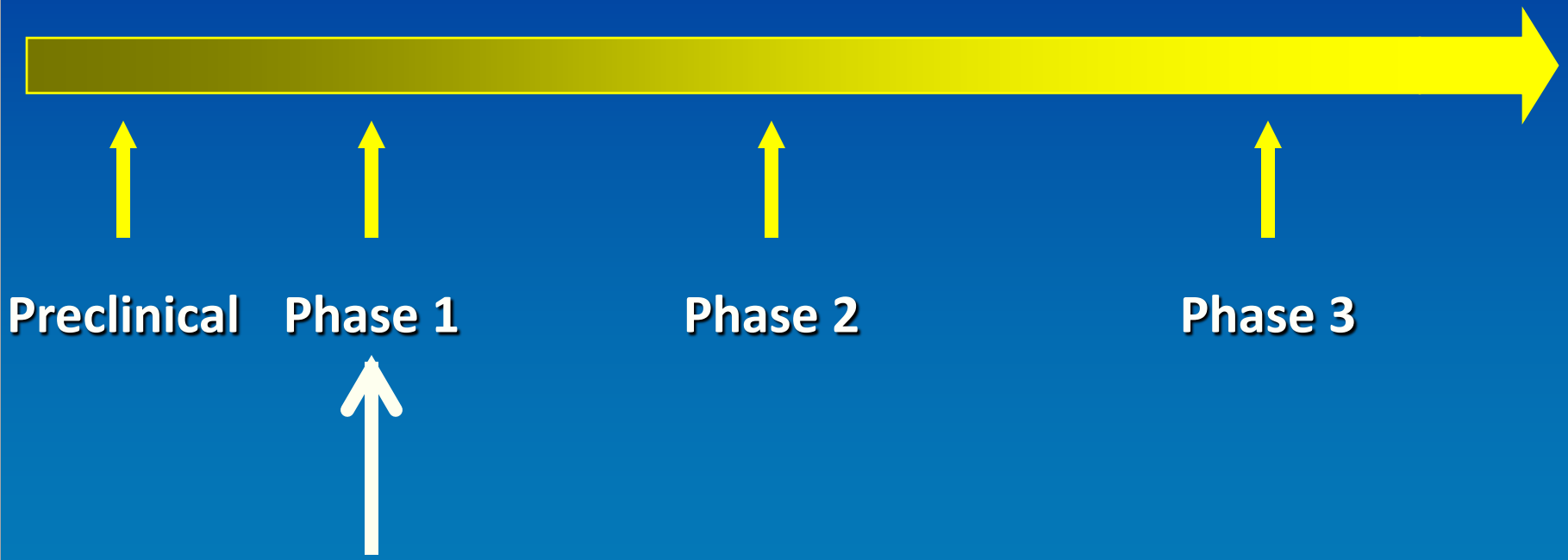
Progression of Trials



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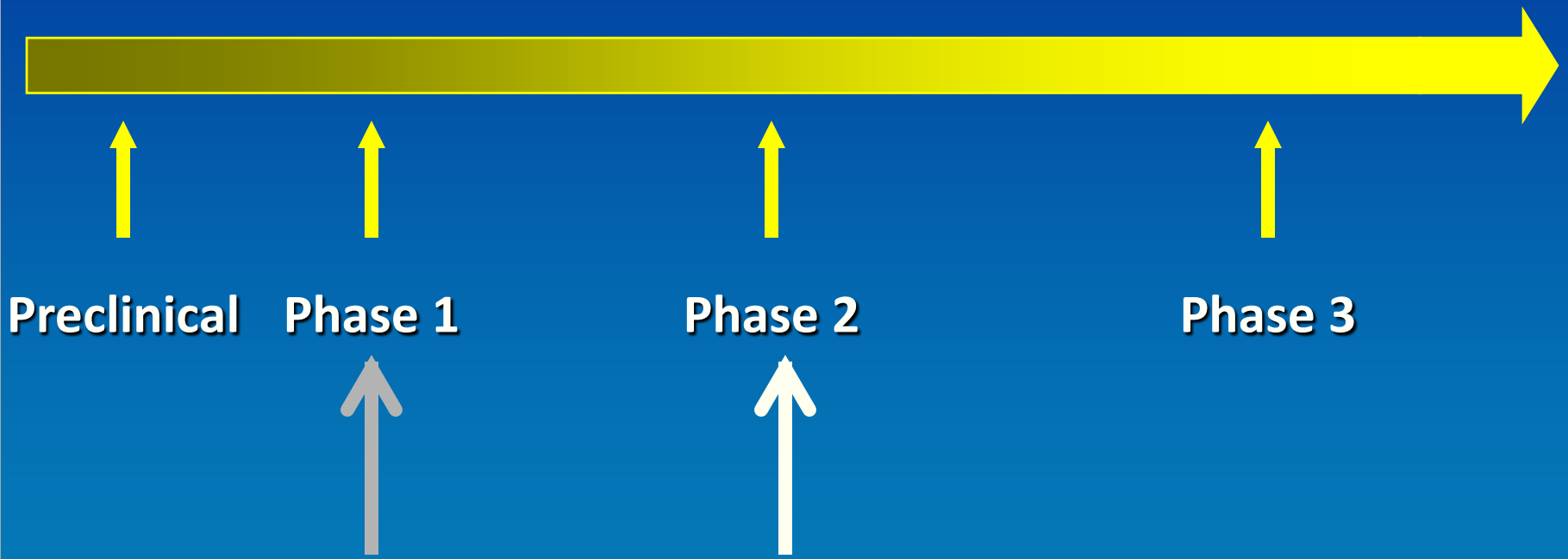
Progression of Trials



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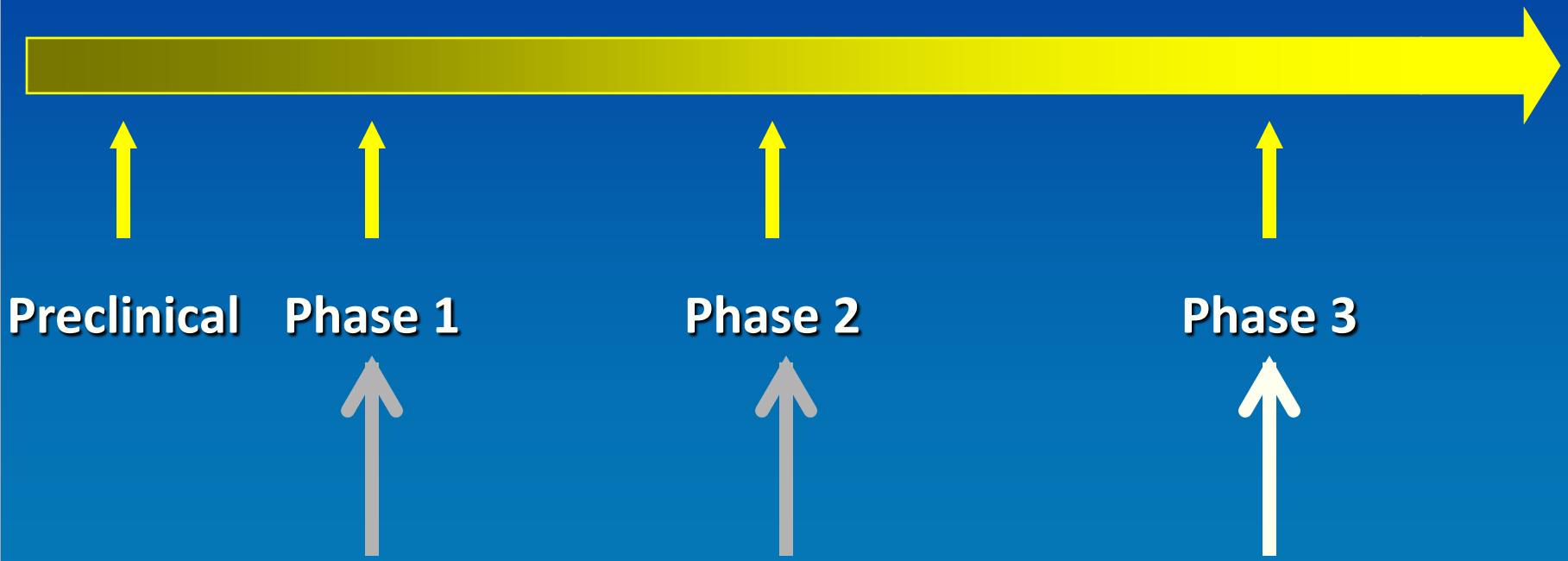
Progression of Trials



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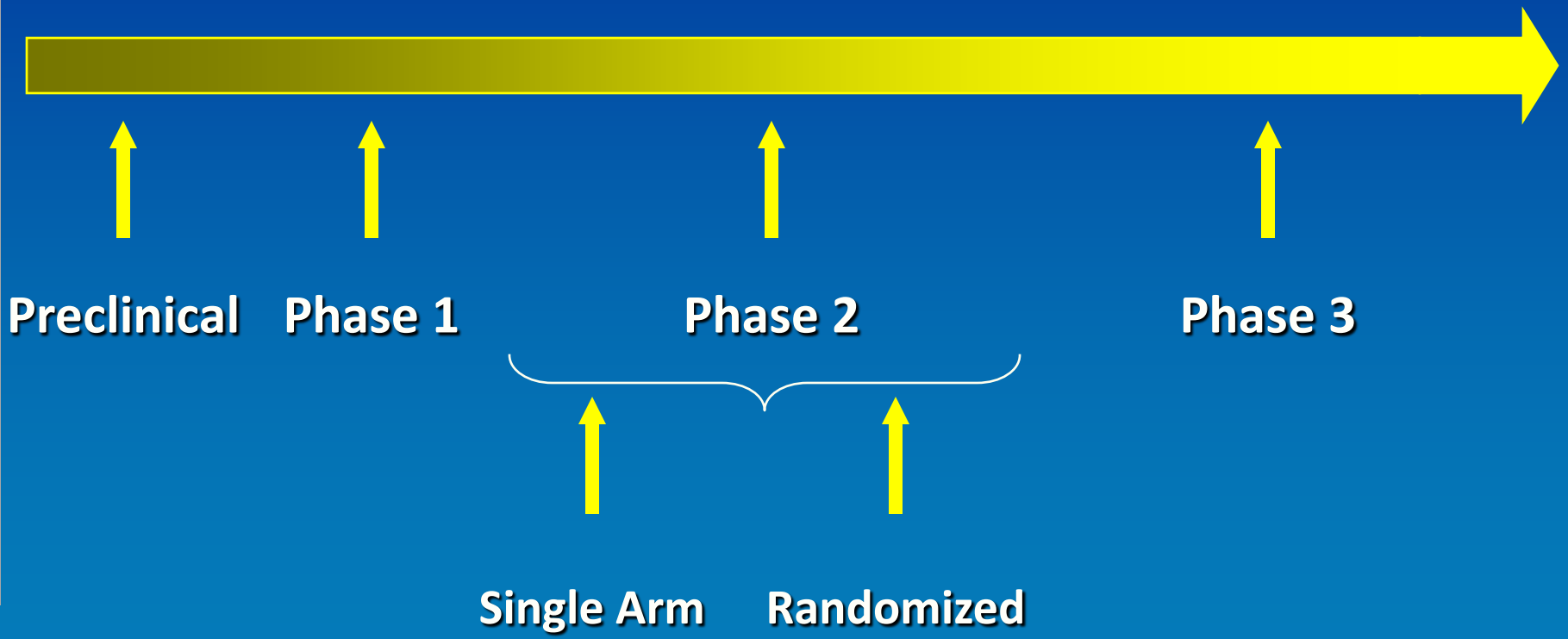
Progression of Trials



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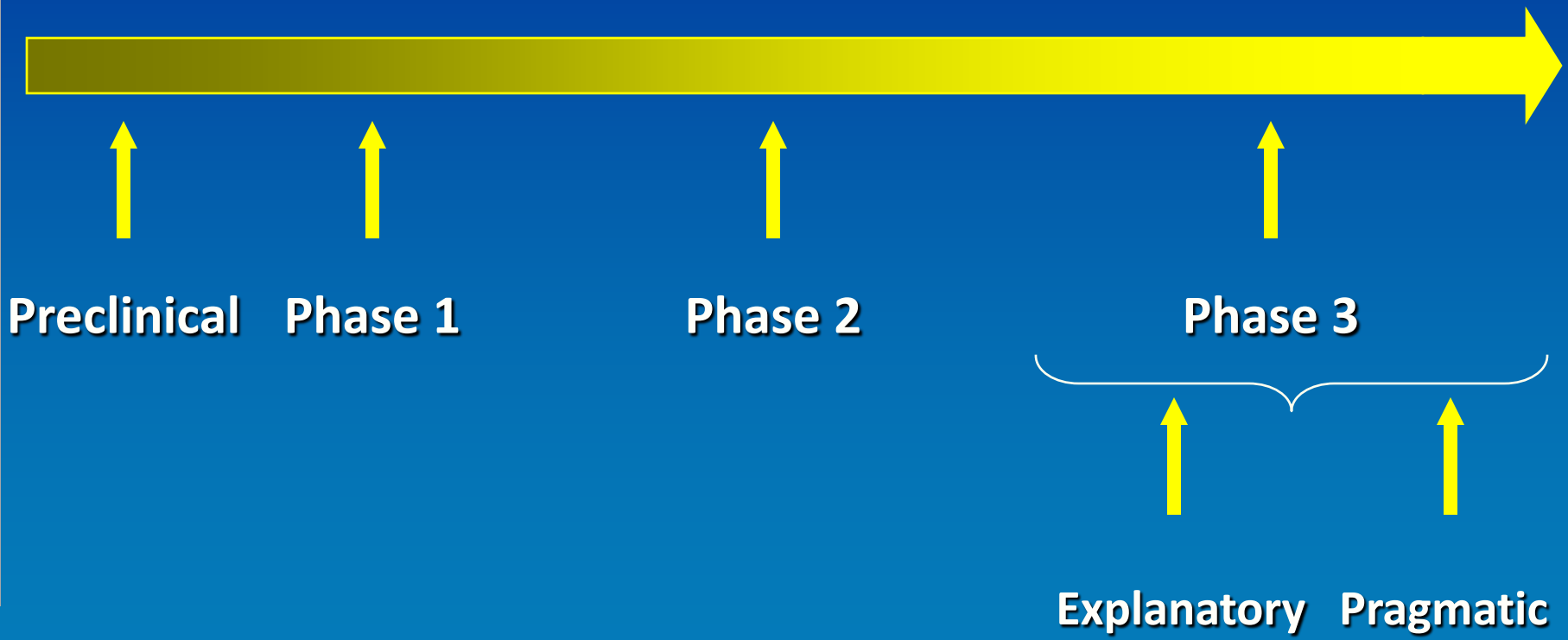
Progression of Trials



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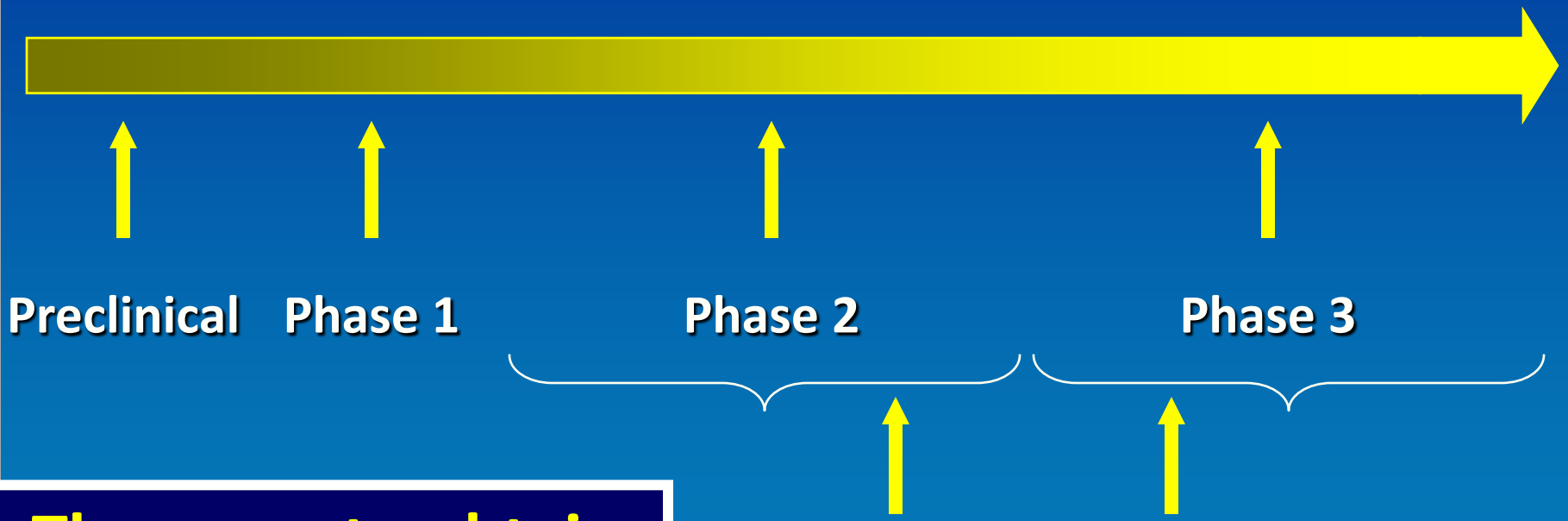
Progression of Trials



These are to obtain signal or to confirm efficacy

Explanatory Trials

- Knowledge of efficacy is necessary
- Causal mechanisms can be better understood, be these biologic or related to care delivery
- Because ‘noise’ is reduced, effect sizes of efficacy can be better estimated
- Regulatory requirements can be satisfied

Explanatory Trials

- Knowledge of efficacy is necessary
- Causal mechanisms can be better understood, be these
- Because 'noise' is reduced, effect sizes of efficacy can be better estimated
- Regulatory requirements can be satisfied

Explanatory trials generally have a reduced risk of bias.

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Pragmatic Trials

- These fit Comparative Effectiveness Research paradigm
- They should be of direct clinical relevance
- Because ‘noise’ is > explanatory trial, superiority results are robust

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Pragmatic Trials

- These fit Comparative Effectiveness Research paradigm
- **Pragmatic trials have enhanced generalizability.**
- Because ‘noise’ is > explanatory trial, superiority results are robust

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Developmental Trials

- Typically developmental trials designed to inform an explanatory RCT emphasize detecting a signal of efficacy:
  - eg, the randomized phase II trial
- Typically developmental trials designed to inform a pragmatic RCT emphasize determining feasibility and evaluations of methodologic issues
  - eg, the pilot phase III trial

In patients with (your disease priority) does (new therapy) improve (relevant outcome) in comparison with (standard therapy)?

Linking Trial Principles to Regulations

If There is A Main Message …

- Clinical trials represent human experimentation
- They are absolutely essential to forward medical science and patient care
- They represent a unique form of patient care and require following the policies and procedures associated with the safe and ethical conduct of human experimentation

Ergo – regulations and protocols are not a series of suggestions

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Glossary - 1

Investigator

- A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator.

Sponsor

- An individual, company, institution, or organization which takes responsibility for the initiation, management, and/or financing of a clinical trial.

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IHC GCP available at http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/ich/efficac/e6-eng.php#a1.0

Glossary - 2

Institutional Review Board (IRB):

- **An independent body constituted of medical, scientific, and non-scientific members, whose responsibility is to ensure the protection of the rights, safety and well-being of human subjects involved in a trial by, among other things, reviewing, approving, and providing continuing review of trial protocol and amendments and of the methods and material to be used in obtaining and documenting informed consent of the trial subjects.**

- **Canada uses term Research Ethics Board (REB)**

IHC GCP available at http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/ich/efficac/e6-eng.php#a1.0

Ethics vs. Regulatory Approvals

Ethics Approval

- Conducted by REBs (local or central or both)
- Mandated by institution, funders, Health Canada

Regulatory Approval

- Conducted by Health Canada
- Mandated by: Clinical Trial Regulations for Drugs
  Medical Devices Regulations
  Natural Health Products Regs

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Determining Your Accountabilities

- These vary by trial
- Considerations include:
  - use of human subjects
  - source of funding
  - intervention studied
  - local/institutional requirements

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Determining Your Accountabilities

- Research Involving Humans
  - Declaration of Helsinki
  - Local REB requirements
- Human Research funded by Canadian federal granting agencies (CIHR, NSERC, SSHRC)
  - Tricouncil Policy Statement
- Human Research funded by US federal funds (NIH)
  - US Federal Regulations re: Human Subjects Protections
  - NIH Guidelines

Determining Your Accountabilities

- Clinical Trials Involving Drugs
  - Canada: Health Canada Food and Drug Act Regulations re: Clinical Trials
  - US: FDA Regulations
  - ICH - Good Clinical Practice Guidelines (ICH-GCP)

Health Canada has separate regulations for devices and natural products

Determining Your Accountabilities

The Health Canada Clinical Trials Application:

"Sponsors must file a Clinical Trial Application (CTA) to conduct clinical trials in Phases I through III of drug development and comparative bioavailability trials. This includes applications to conduct clinical trials involving marketed products where the proposed use of the product is outside the parameters of the authorized Notice of Compliance (NOC) or Drug Identification Number (DIN) application (e.g. using a marketed product for a 'new' indication or using an unauthorized dose etc)."

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http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/clini/cta_background-eng.php

Determining Your Accountabilities

The Health Canada Clinical Trials Application:

- CTA Trials must follow *International Conference on Harmonization Good Clinical Practice* (GCP).
- You thus need to understand requirements of:
  - The REB
  - The Investigator
  - The Sponsor
  - The Clinical Trial Protocol and Amendments
  - The Investigator Brochure
  - Essential Documents for the Conduct of a Clinical Trial

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http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/ich/efficac/e6-eng.php

The Investigator

The Sponsor

and …

The Sponsor

and …

The Sponsor

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and, finally …

The Sponsor

In patients with (your disease priority) does (new therapy) improve (relevant outcome) in comparison with (standard therapy)?

Linking Principles to Roles and Responsibilities

If There is A Main Message …

- Contracts are developed so that responsibilities and roles are clear
- They are required because stakeholders come from different perspectives and have different interests and accountabilities
- While collaborations develop because of mutual interests, there will not be complete overlap in these interests

Ergo – you will need contract advice that includes access to legal expertize

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Standard NCIC CTG "Contracts"

- Participating Centre Agreement
- Intergroup Roles and Responsibilities Template
- Contracts with Industry
- Trial Specific:
  - Data Sharing Policy
  - Polices for Access to Biospecimens

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Roles and Responsibility Documents (Text)

1. Conduct of the Trial
2. Duties … of NCIC CTG
   … of (collaborator)
3. Indemnity
4. Access to Trial Data and Publication
5. Intellectual Property
6. Term and Termination of the Agreement
7. Confidentiality
8. Miscellaneous

Roles and Responsibility Documents (Table)

- Protocol
- Amendments
- Contracts
- CRFs
- Informed Consent
- Regulatory Authority (including safety)
- IMP
- Ethics Activities
- Investigator Selection
- On-site A+M
- Informed Consent
- Centre Activation
- Investigator Meetings
- Data Management
- Trial Close Out
- Stats Analysis / Report

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The Big Three

- Indemnification
- Intellectual property
- Confidentiality

Note: Publication is now generally straightforward

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In patients with (your disease priority) does (new therapy) improve (relevant outcome) in comparison with (standard therapy)?