Clinical trials: Prerequisites

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Disclosures

- Research Funding
  - Pfizer
  - Novartis
  - GSK
  - Entremed
  - Karyopharm
  - Amgen
  - Bayer
  - Bristol Myers Squibb
  - Roche

Objective

- To understand the pre-requisites of conducting a clinical trial
  - Practical approach
  - Interactive – please ask questions as I go along or in Q&A session
  - Modeled on **early phase** clinical trials **with sponsorship**, unless indicated otherwise.

Clinical Scenario

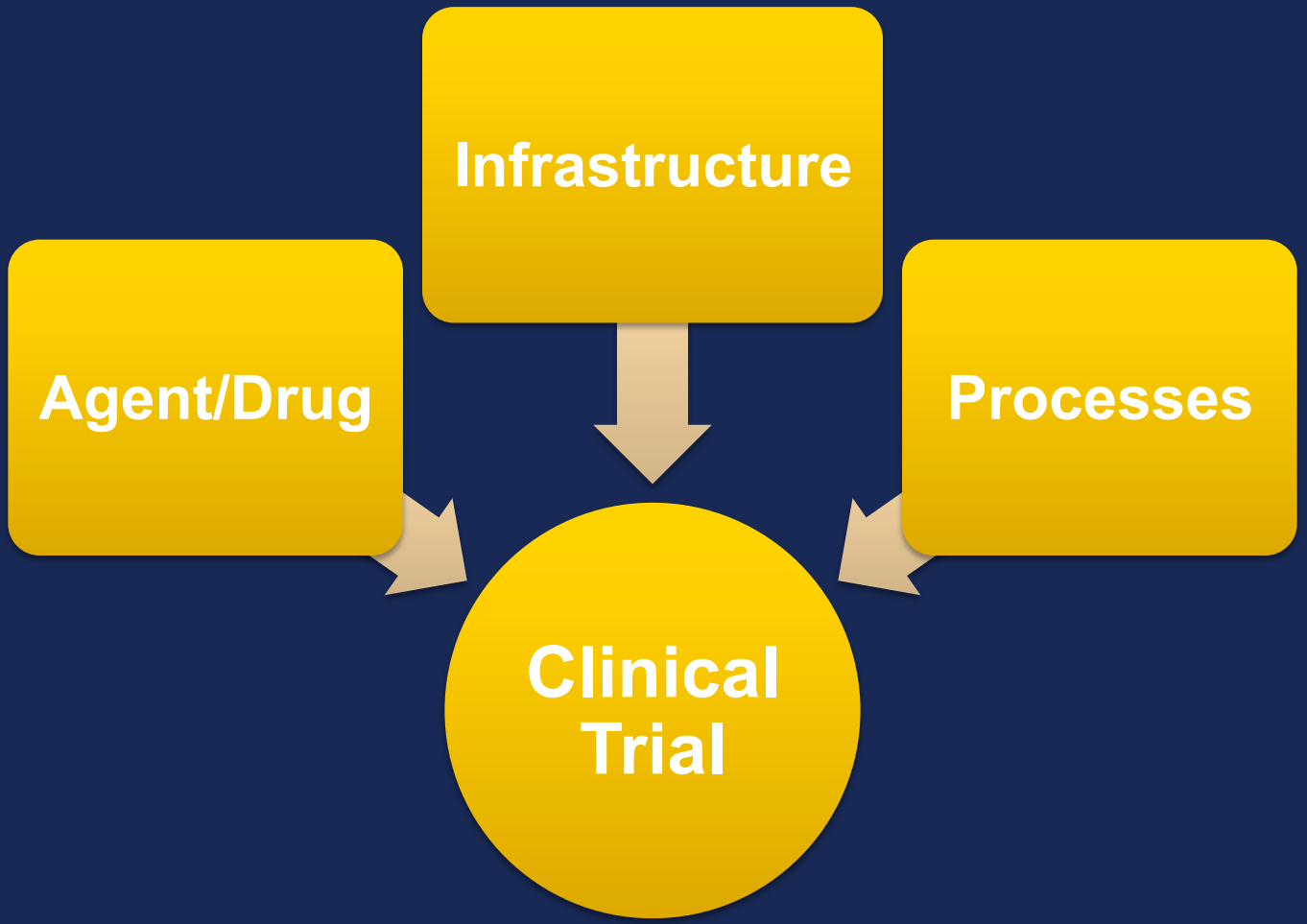
- A scientist from a lab in your University approaches you about a drug he has discovered by high throughput screening of agents that targets the product of a new oncogene CUREALL-1
- Works amazingly *in vitro* and *in vivo* in a cancer cell line
- No effects on benign fibroblasts
- No bad effects on the mice during the *in vivo* experiments
- They have 1 kg of the stuff ready to go
- Wants you to take drug into humans now

What do you do??

Clinical Scenario

- You have been approached about a drug called CUREALL-1
- According to the person who approached you, this is a miracle drug in the lab and wants you to take it to the clinic
- Ironically, this is the first trial that you will be conducting as a PI.
- What do you do?

Getting a clinical trial off the ground



The Drug

- Target
- MOA of Drug
- Efficacy Data
- Safety Data
- Biomarker Data

The Target

- Biologically plausible: evidence that the target is important
  - Effects of knock-in/knock-out experiments
  - Role in pathogenesis of the disease
    - E.g. Bcr-Abl, c-KIT, VHL
  - Expression in clinical specimens
    - Which cancers, what percentage, what pattern
  - Prognostic/predictive
  - Previously successful drugging of target/pathway

The Target

- Can be known and important but not specifically relevant to cancer biology
  - Microtubules
- May not be known
  - Mechanism of action was imprecisely known for many currently used chemotherapy agents
  - High-throughput screening of natural compounds for cytotoxic/cytostatic activity

The Target

- Impacts on trial design
  - Go/No Go
    - Potentially worthwhile to take forward?
    - Well defined biology
    - Me too target
  - Patient population
    - All comers vs. enriched for tumour or target
    - Resistant vs. naive populations

The Drug

- Production
  - GMP (Good Manufacturing Practise)
    - Minimum set of standards for manufacturing
  - Sufficient quantities, practical dosage forms
- Chemistry
  - Chemical class of the agent
    - E.g. Small molecule, antibody, antisense, peptides, natural product, analogue
    - Implications for preclinical testing
      - Toxicity
      - Efficacy
  - Formulation issues

The Drug

- Absorption
  - Oral, IV
- Distribution
  - Sites of action
  - Tissue concentrations: reservoirs, blood brain barrier
- Metabolism and Excretion
  - CYP enzymes, metabolites, route/organs of excretion
- Pharmacokinetic profile
  - Maximum concentration (C_{MAX}), Exposure (AUC), Half-life (blood, tissue), Distribution
  - Accumulation and multiple dose effects
  - PK-Toxicity associations
  - PK-Efficacy associations

The Drug

- Impacts on trial design
  - Route and method of administration
  - Schedule
  - Eligibility criteria
    - Renal and hepatic function
  - Concomitant medications
  - Selection of RP2D
    - MTD
    - PK
    - Efficacy

CUREALL

- Novel agent that results activation of tumor suppresor proteins (TSP).
- TSP inactivation is seen in a variety of cancers
- Small molecule against “TSP blockers”
- Orally bioavailable
- PK data showed a linear, dose dependant pattern

Efficacy Studies

- Will it work? Does the agent effect the target?
  - *in silica, in vitro, in vivo*
  - Target/pathway: expression, phosphorylation
  - Downstream effect: apoptosis, angiogenesis, proliferation
  - Dose/plasma level vs. target/pathway inhibition vs. downstream effects
  - Compare to other agents especially if analogue or similar mechanism of action
  - Combination studies

Efficacy Studies

- In vitro
  - Broad array of well characterized cell lines (e.g. US NCI 60-cell line panel)
  - Determine concentration and exposure effects (IC50)
    - Proliferation (e.g. colony forming assay)
    - Viability (e.g. MTT assay)
  - Explore mechanisms of resistance

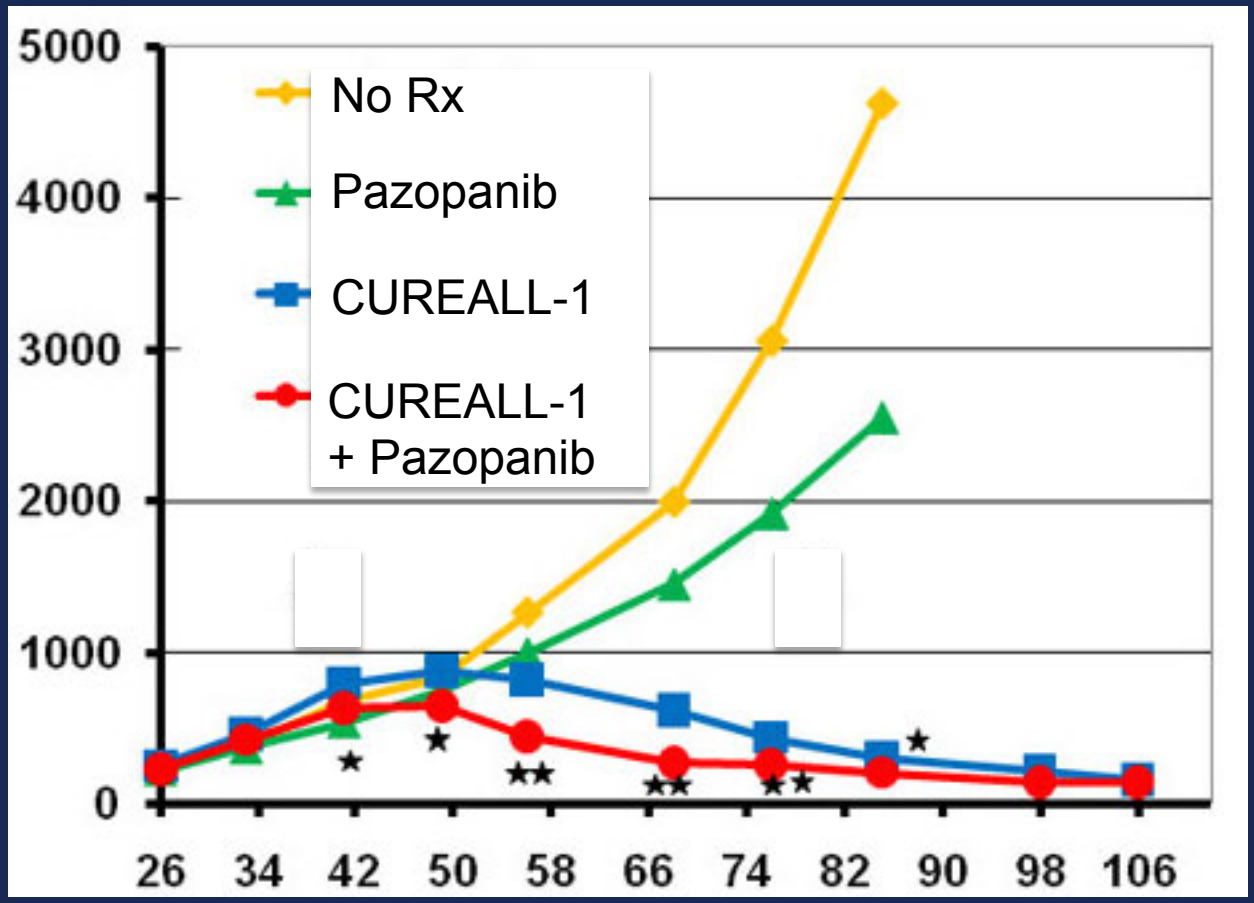
In Vivo Models/Parameters

Parameter	***Variables***
Murine host	Immune competent mouse Immune deficient mouse (nude or SCID mouse) Transgenic mouse
Type of Tumour	Allograft cell line Human Xenograft cell line Spontaneous (e.g. in transgenic mouse)
Tumour Profile	Characterised with respect to key targets Not characterised
Tumour location	Subcutaneous Intraperitoneal Orthotopic Subrenal capsule Hollow fibre
Drug route of administration	Oral Intravenous Intraperitoneal Intratumoural

In Vivo Models/Parameters

Parameter	***Variables***
Drug schedule	Continuous (daily) Single dose Intermittent (e.g. days 1, 5, 9) Repeat dose (e.g. days 1-5)
Drug Dose	Single or multiple dose levels Include MTD for each schedule or other doses
Timing of drug administration	At same time as tumour implantation After implanted tumour is established/palpable After implanted tumour has micrometastases After implanted tumour has macrometastases After resection of implanted tumour (“adjuvant”)
Measures of efficacy	Tumour regression Tumour growth delay (%T/C) Animal survival Animal cures (or proportion long term survival)

CUREALL-1: Efficacy



Non-Proprietary Figures: For Illustration Only

Efficacy: General Considerations

- No mandated studies
  - Up to the company and investigators
- Not predictive of success
  - Immortal, stable, homogenous, rapidly proliferating
  - But a high negative predictive value
- Want to have:
  - Multiple xenograft models (>2)
  - Models that establish the tumour +/- metastases prior to treatment
  - Models that use IV or PO administration
  - Dose response effects: plasma level–target–tumour
  - Comparisons, combinations

Efficacy Studies

- Impact on trial design
  - Go/No Go:
    - Interesting enough to take forward?
    - Best compound to take forward?
    - Better than current standard?
  - Drug combinations
  - Tumour types

Required Toxicology

Type of toxicology	Requirements

Single Dose	• 2 species: rodent & non-rodent
	• Clinical formulation
	• Several doses studied
	• Determine toxicity and organ effects
	  • NOAEL, LD10
	• PK for relationship to exposure and effects
	• Species specific if required
	  • Target
	  • Toxic effects

Repeat dose	• 2 species: rodent & non-rodent • Clinical formulation, dose and schedule • Several dose levels • Duration of treatment same as planned treatment duration in clinic • Determine highest doses that can be safely administered, organ effects, severity and reversibility • Species specific if required

Required Toxicology

Type of toxicology	Requirements

Chronic Toxicity	• 2 species: rodent and non-rodent
	• Clinical formulation, dose and schedule
	• Duration of treatment:
	  • Rodents: 6 months
	  • Non-rodents: 9-12 months
	• Determine chronic or late effects of treatment and their severity, reversibility
	• May not be necessary prior to phase I

Safety pharmacology	• Evaluation for specific major organ effects • Test system depends on organ system of concern or interest. • Basic battery: cardiovascular, respiratory, CNS
Genotoxicity	• In vitro tests for mutations and chromosomal damage from the experimental agent.
Local toxicity	• Assessment of local tolerance using routes relevant to method of administration

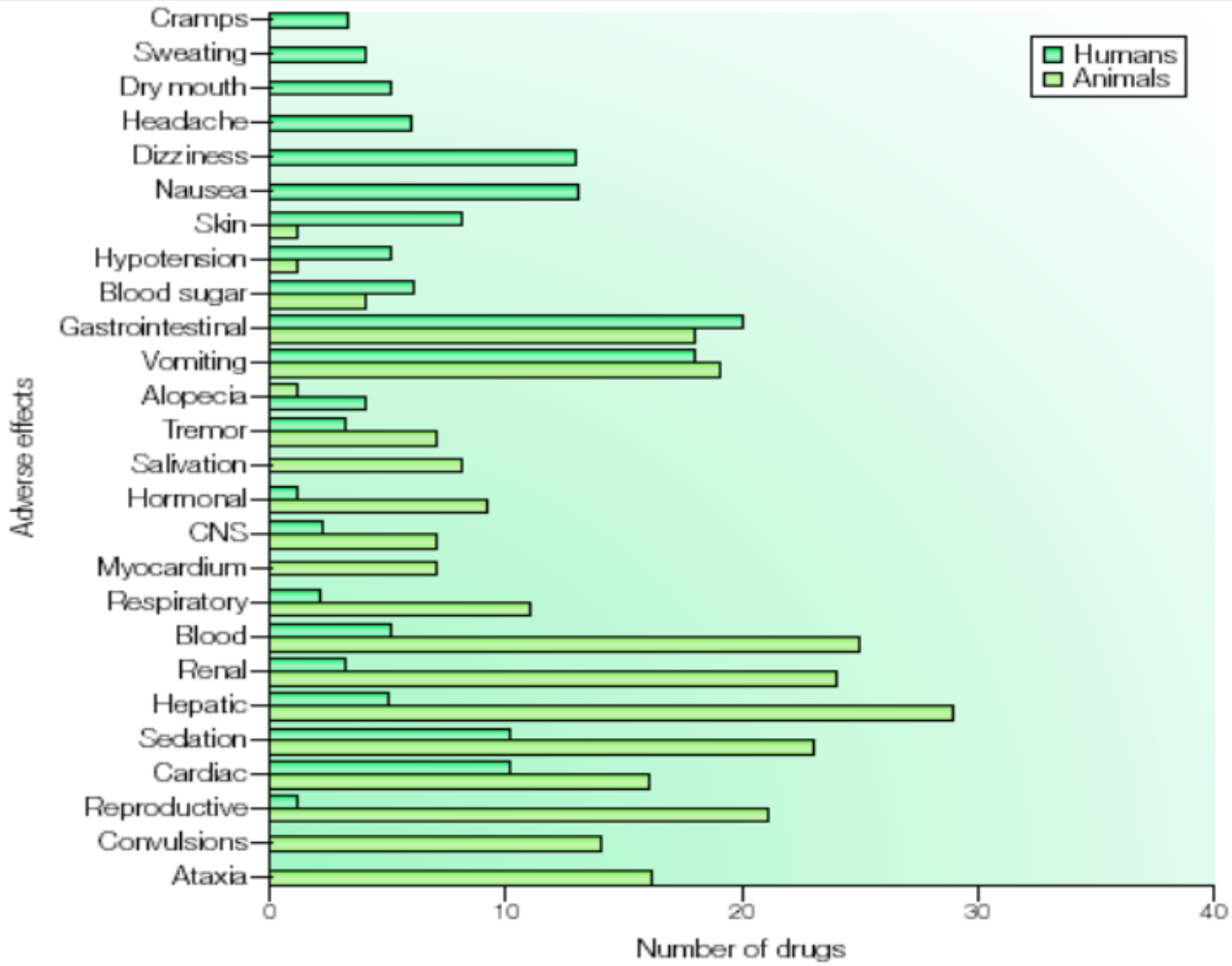


Figure 1 | **Animal and human toxicities of 45 drugs assessed by the Committee on Safety of Medicines in the United Kingdom during the eight or nine months prior to publication in 1978** (REF. 11). Data are for drugs of diverse therapeutic classes, including several cardiovascular and central nervous system drugs but only one anticancer agent. The six uppermost adverse effects were observed in humans but not in animals; the two adverse effects at the bottom of the graph were observed in animals but not in humans. For most adverse effects there is a degree of over- or under-prediction. CNS, central nervous system.

Greaves, Nature Drug Discovery, 2003

Biomarker Assay

- Biomarker
  - Factor that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention

Biomarker Assay

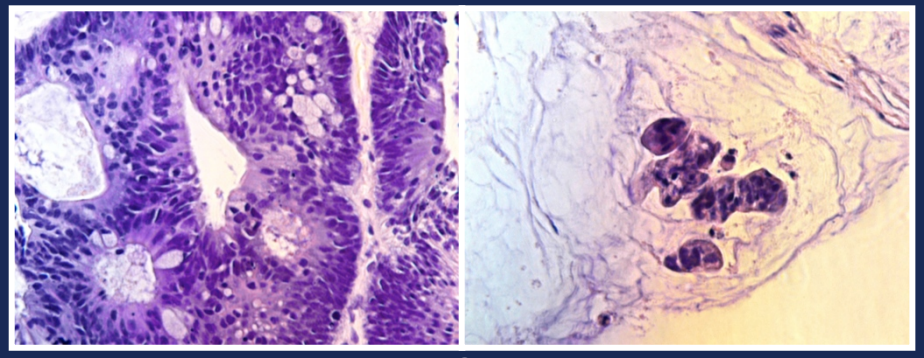
- Biomarkers in clinical trials
  - Proof of principal biologic activity on target in a patient
  - Optimization of dose and schedule (vs. MTD or PK)
  - Predictive marker for selection/stratification
  - Surrogate endpoint of clinical benefit

Biomarker Assay

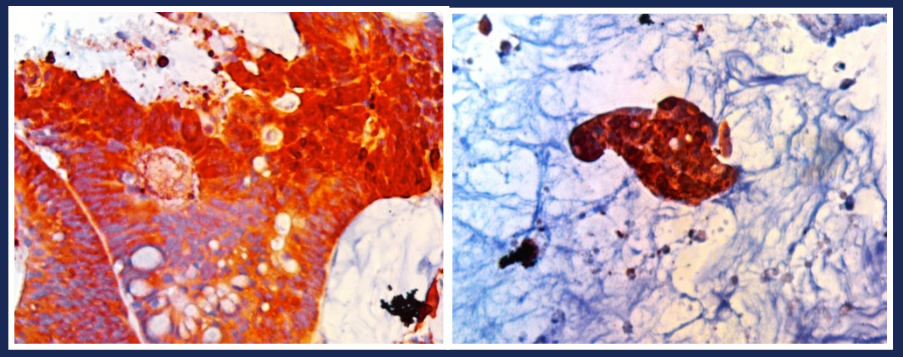
- Considerations
  - Assay performance
    - Accuracy, reproducibility
    - Qualitative vs. quantitative
    - Limits of detection
    - Handling processes optimized and characterized
  - Relationship between biomarker assay vs. dose/PK vs. anti-tumour efficacy
  - Time course: duration, recovery
  - Tumour vs. other tissues

Biomarker: CUREALL

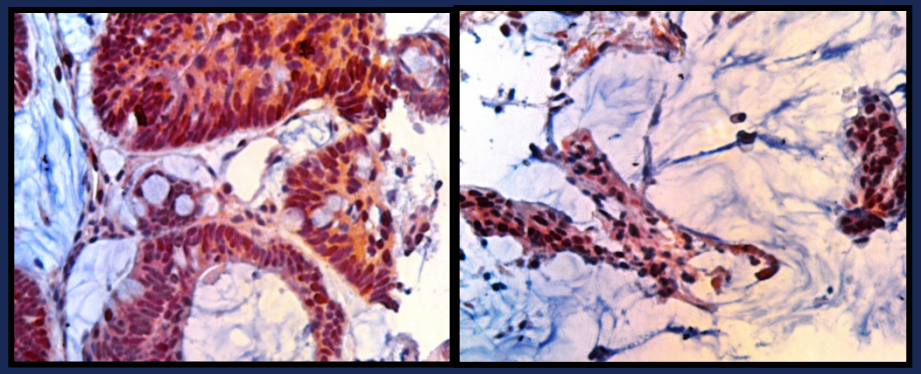
3 weeks: less tumor cellularity and increased nuclear retention for IκB, p53 and FOXO1



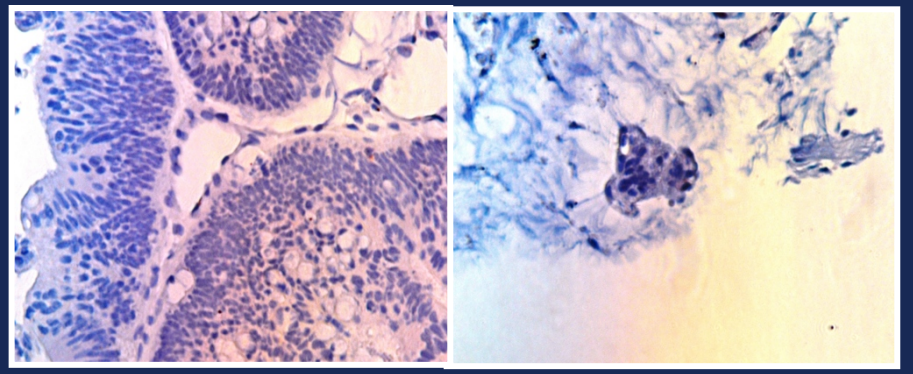
Pre-Treatment H&E 3 weeks



Pre-Treatment IκB 3 weeks



Pre-Treatment p53 3 weeks



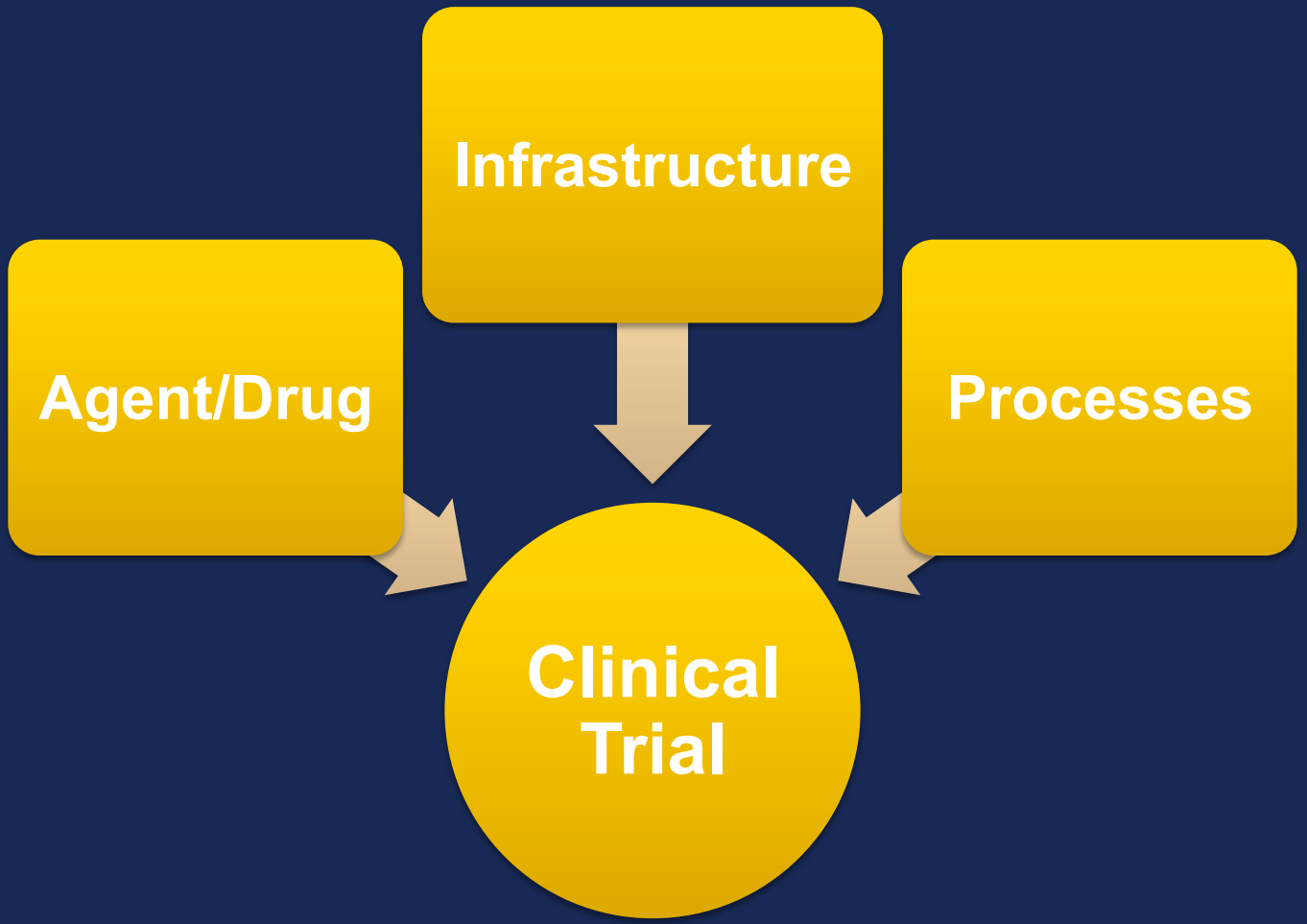
Pre-Treatment FOXO1 3 weeks

Non-Proprietary Figures: For Illustration Only

Biomarker Assay

- Impact on clinical trial design
  - To do or not to do? Will it provide useful information?
    - Increased complexity and cost
    - Limited patient numbers
    - Assay performance
  - Selection of patients
  - Timing of studies
  - Tissues to be sampled
  - Dose levels to include
    - All dose levels vs. 1 or 2 dose levels

Getting a clinical trial off the ground



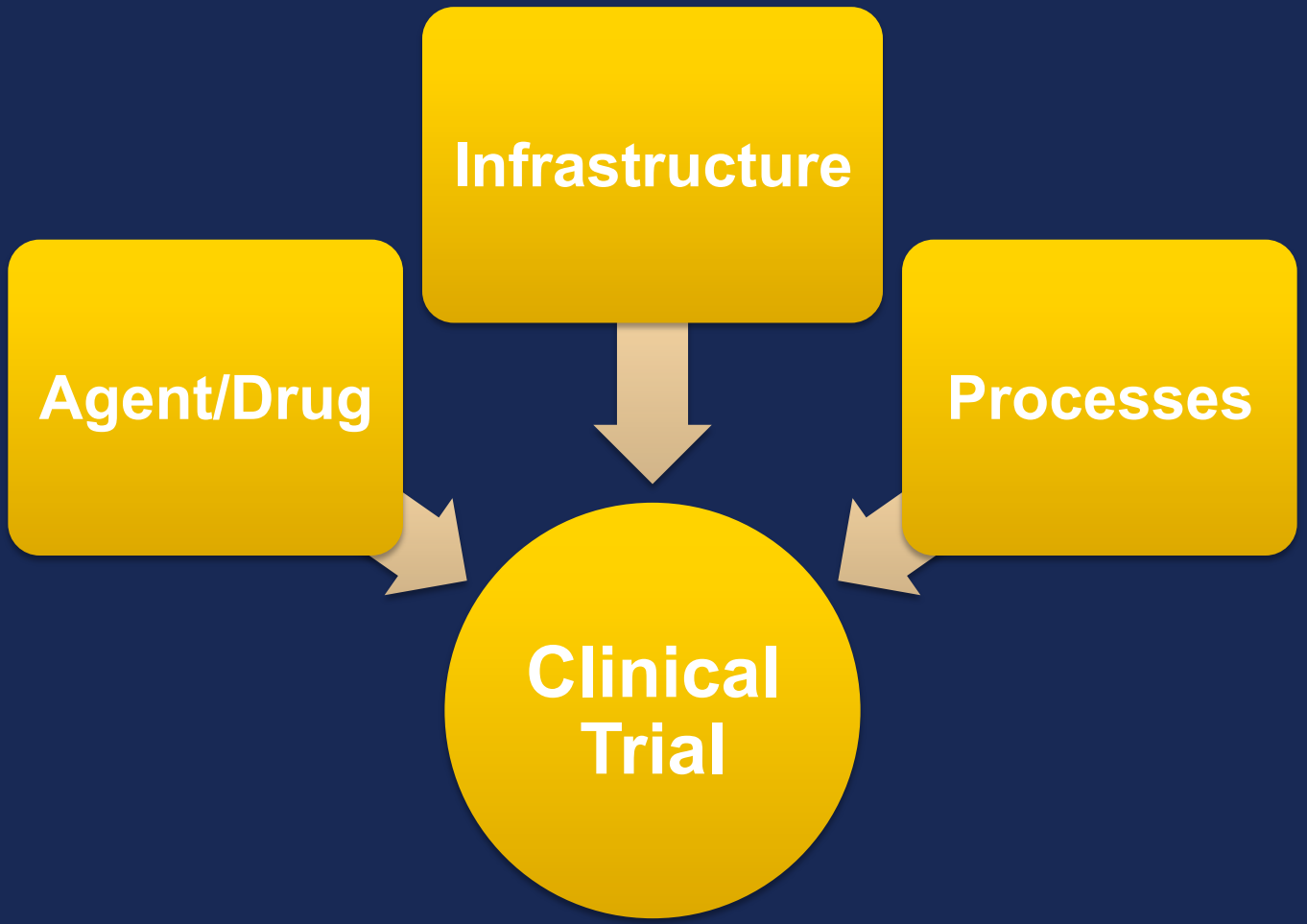
Personnel

- Your research program's success depend on the "buy-in" from your team:
  - Other investigators:
    - Oncologists, laboratory scientists, pathologists, radiologists, etc.
  - Trial nurses, clinical research associates
  - Pharmacists
  - Biostatisticians
- Meet with them regularly and tell them what's happening!

Resources - institutional

- Grants and contracts services (GCS)
- Research financial services (RFS)
- Technology development and commercialization (TDC)
- Institutional review board/research ethics board/ethics committee (REB)
  - Protocol review committee
- Impact assessment (e.g. radiology, pathology, nursing, chemodaycare, etc)

Getting a clinical trial off the ground



Types of diagnostic or therapeutic interventions involving human subjects (e.g. clinical trials) – *full-board REB review*

1. Investigator-initiated
2. Academic agencies e.g. US NCI (US National Cancer Institute), NCIC (National Institute of Canada)
3. Pharmaceutical industry-initiated

Clinical Trials – Funding vs Sponsorship

	Protocol Development	Funding		Sponsorship (related to safety reporting)
		Drug	Per case	
Investigator-initiated	Investigator	Company	Company Grant Other sources	Usually investigator or research program
NCIC	NCIC with input from investigators	Company	NCIC	NCIC
US NCI	Investigator with input from US NCI	US NCI	US NCI gives grant to centre	Research program (e.g. DDP)
Industry	Industry with input from investigators	Company	Company	Company

Step-by-step guide to activating a clinical trial – 1

- Concept → protocol development
- If company trials, usually need you to sign a CDA (confidential disclosure agreement), once a confidential non-disclosure is established, review the protocol in detail, and asks key individuals in your research team for input
- Protocol review committee (if any)

Step-by-step guide to activating a clinical trial – 2

- Key questions you need to ask before deciding to take part:
  - Do you have enough patients to put on the trial?
  - Do you have any competing trials?
  - Do you have the personnel to run the trial?
  - Do you have the resources and infrastructure to run the trial (e.g. electronic data capture; IV pumps; treatment space; freezers, etc)?

Step-by-step guide to activating a clinical trial – 3

- Once you decide to participate in a study, the following processes should be activated:
  - Grants and contracts office – existent templates would expedite contract review
  - Budget – you (or someone familiar with the costs of procedures and tests in your institution) need to review this carefully
  - REB submission

Example of budget items – don't forget the overhead XX% (indirect costs)!

Procedures
Administrative Cost per Patient Visit (Including Nursing)
Adverse Event / Toxicity Assessment (Average)
Biopsy - Procurement
Biopsy - Processing
Blood Sample Collection - Pharmacokinetic (PK)
Blood Sample Processing - Pharmacokinetic (PK)
Blood Sample Processing / Shipping
Blood test-Other
Concomitant Medication Assessment
Research Coordinator For Data Management
CT scans Above Standard of Care
ECG / EKG / Electrocardiogram
MUGA or ECHO
Pharmacy Services
Archival Tissue Sample Collection
Tumour Response Assessment (RECIST)
TOTAL

Total Plus XX% Overhead

One Time Financial Events (All Sites)
REB Initial Local Submission and Annual Renewal
Document Archiving
Pharmacy Fees (Start-Up)
Pharmacy Fees (Annual) x 5
Study Start-Up (Average)
Study Close-Out

Step-by-step guide to activating a clinical trial – 4

- Health Canada submission for a Clinical Trials Application (CTA):
  - Pharmaceutical-sponsored – done by company or by a Clinical/Contract Research Organization (CRO)
  - Investigator-initiated research (IIR) – you may have to do this yourself!
  - Academic agency-sponsored (e.g. NCIC, RTOG, etc) – done by the sponsor usually the academic agency itself. For US NCI trial done by the DDP – done by DDP. Typically done prior to or concurrent with REB submission

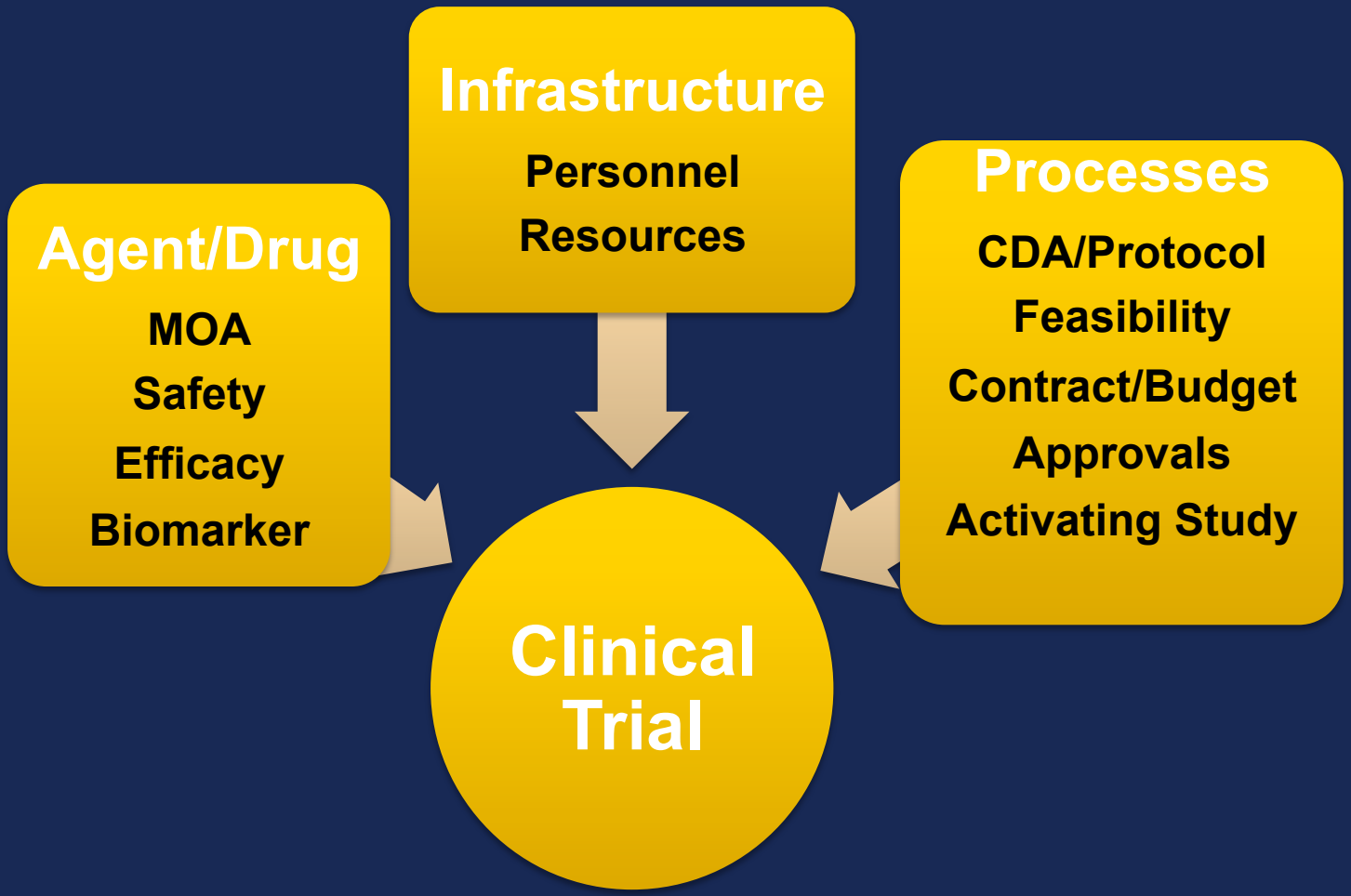
Step-by-step guide to activating a clinical trial – 5

- Collecting documents prior to trial activation:
  - PI and investigator CVs, GCP certificates
  - Lab licenses/certificates, normal ranges
  - Financial disclosure agreements

Step-by-step guide to activating a clinical trial – 6

- **Site initiation visit (SIV)**
  - Personnel/signature log
  - Drug and protocol review
  - Investigator responsibilities
  - Patient enrollment procedures
  - Serious adverse event reporting
  - Handling and shipment of biological samples
  - Drug shipment, storage, dispense
  - CRF completion

Getting a clinical trial off the ground



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