Organizing a Phase I Unit: The Dos and Donts

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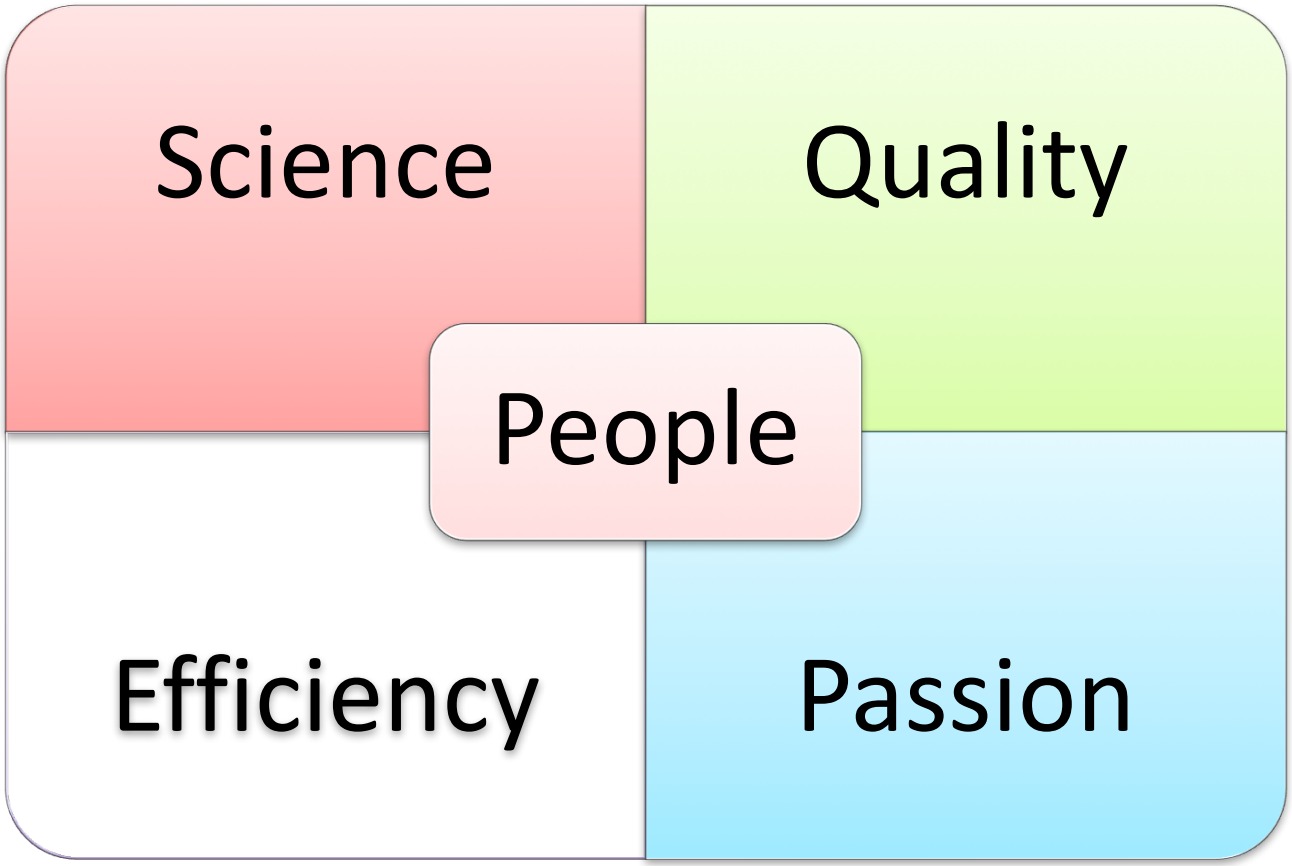
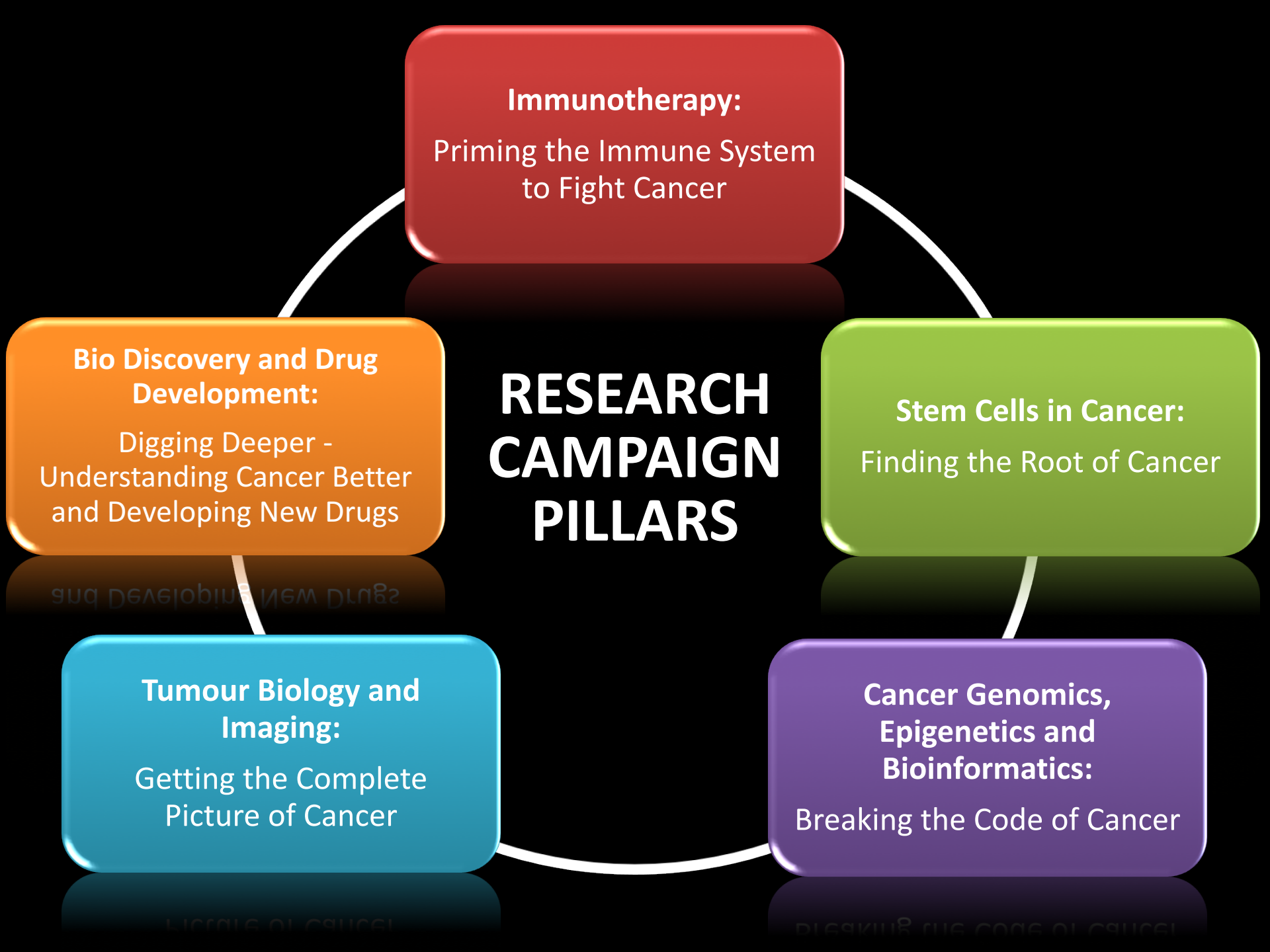
UHN Princess Margaret Cancer Centre

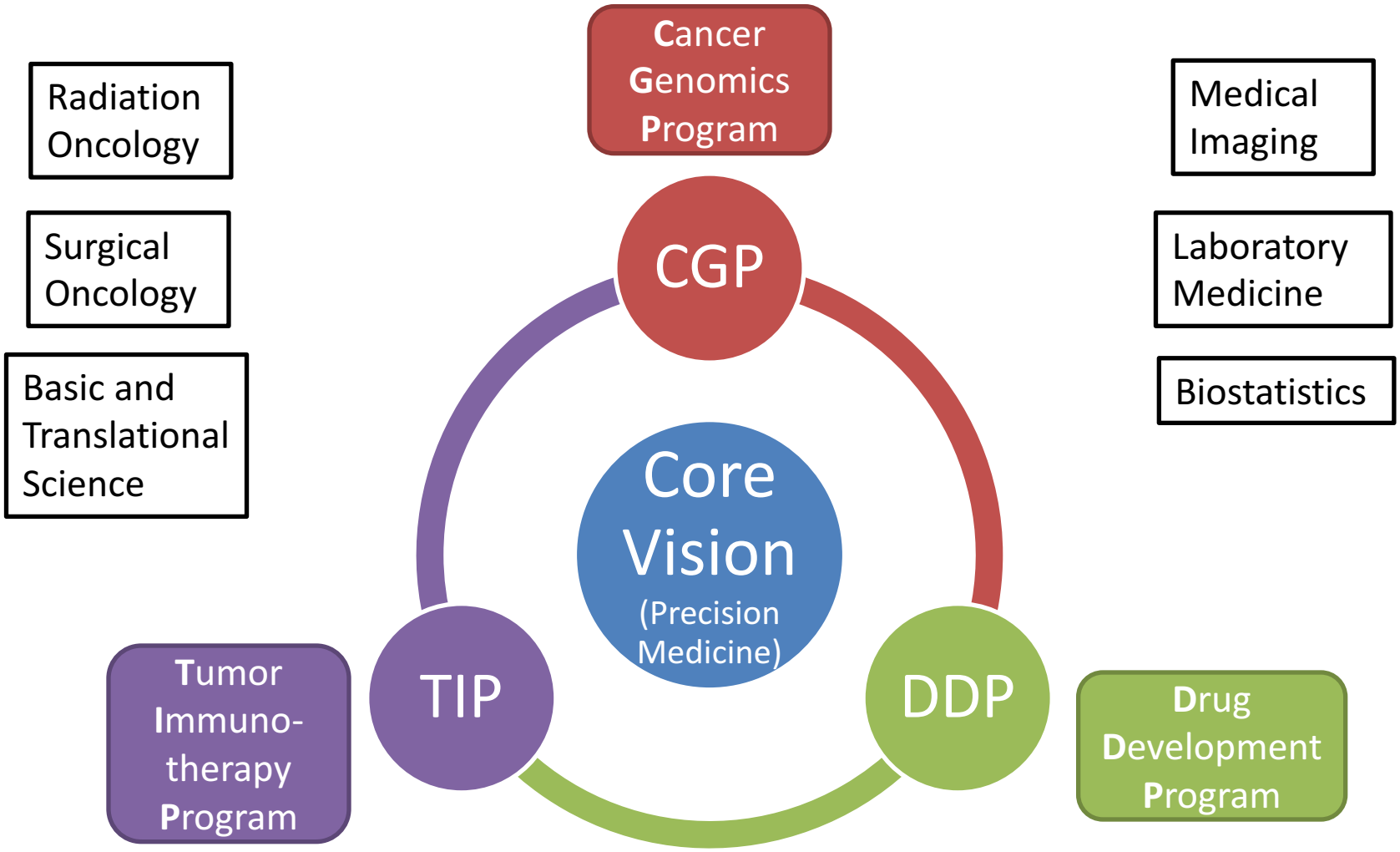
It’s About Building Bridges

Building Bridges for Research: The Most Important Elements




Immunotherapy:
Priming the Immune System to Fight Cancer
Stem Cells in Cancer:
Finding the Root of Cancer
Cancer Genomics, Epigenetics and Bioinformatics:
Breaking the Code of Cancer
Tumour Biology and Imaging:
Getting the Complete Picture of Cancer
Bio Discovery and Drug Development:
Digging Deeper - Understanding Cancer Better and Developing New Drugs
RESEARCH CAMPAIGN PILLARS

Vision for a **Triad of Synergy** to form a **Precision Medicine Enterprise**



Phase I Program at Princess Margaret

- Largest early drug development program in Canada
- One of 12 cancer centres (11 extramural, 1 intramural) selected by U.S. NCI to receive a Phase I UM1 grant
- Excellent training group for young investigators – many ultimately return to home country to build their own drug development programs
- Active clinical and translational research: Genomics and epigenetics, immuno-oncology, pharmacodynamic biomarkers of novel molecularly targeted agents, tumor xenografts from fresh tumor biopsies

Phase I Program at Princess Margaret

- **Preferred partnership with multiple pharmaceutical companies – expertise in first-in-man clinical trials including molecularly targeted and immuno-oncology agents**
- **Rapid start-up time (from protocol receipt to study activation is about 60-70 days)**
- **Average accrual to phase I program (solid tumors) is 200-250 patients per year**

Phase I Program at Princess Margaret

- **Phase I team work meeting every week**
- **Dedicated weekly Phase I clinic**
- **Short-term admission unit utilized to meet inpatient needs** (i.e. pharmacokinetics, monitoring, etc)
- **Start up meeting and regular dose escalation decision teleconferences for each trial**
- **Standard operating procedures in place, regular internal audits and monitoring for NCI-CTEP and investigator initiated studies**
- **Contracts are handled by dedicated person who works specifically on phase I trials and the Drug Development Program so that time line is short (especially if we are designated to have FPFV)**

CANCER GENOMICS PROGRAM

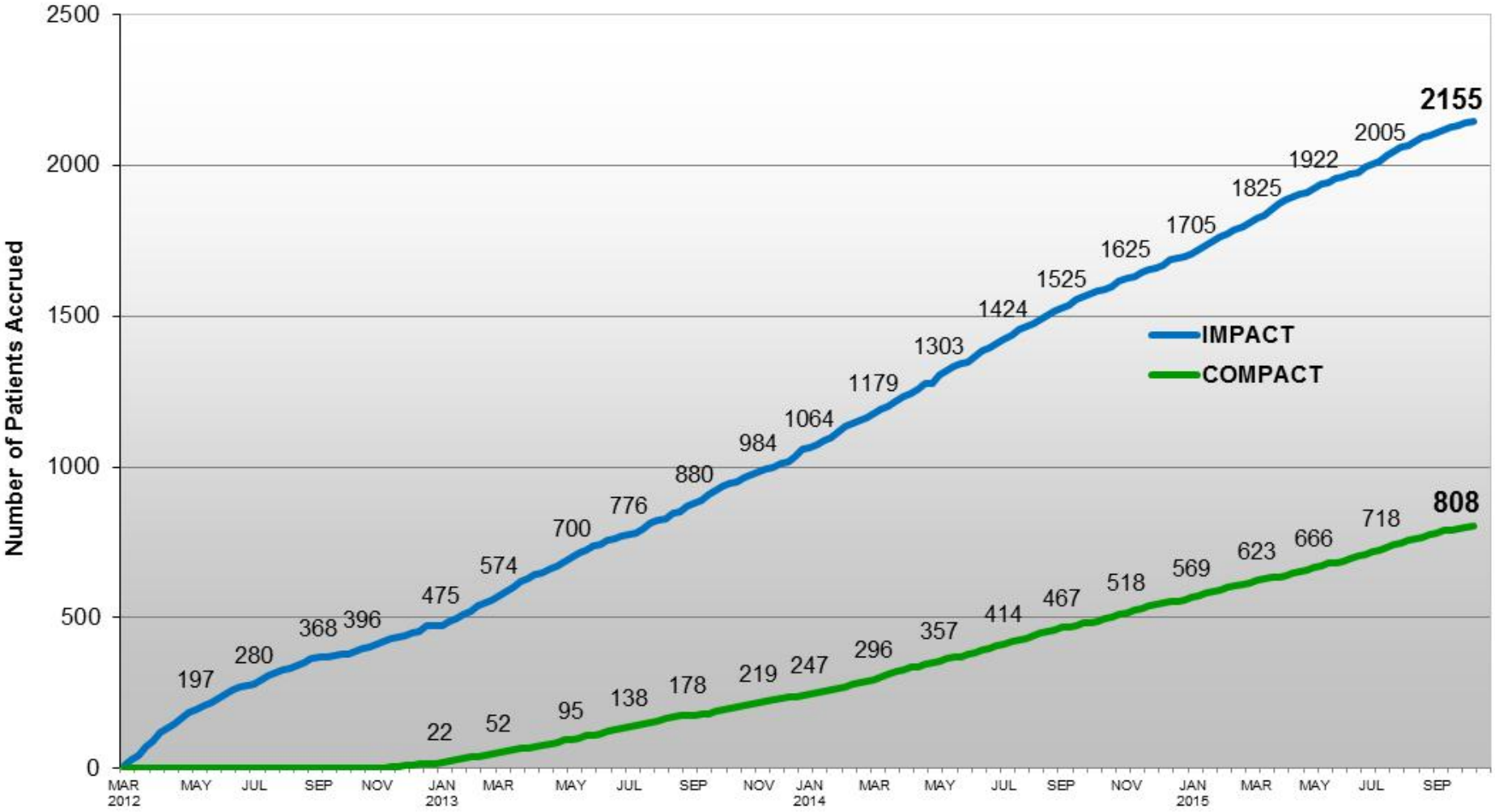
Cancer Genomics Program (CGP)

Clinical Director: Phil Bedard **Scientific Director: Suzanne Kamel-Reid**
Executive Director: Lillian Siu

The **mission** of the **CGP** is to advance personalized/precision cancer medicine through the identification of genetic mutations and molecular mechanisms that drive cancer, to match patients to targeted therapies based on their genotype and to predict prognosis.

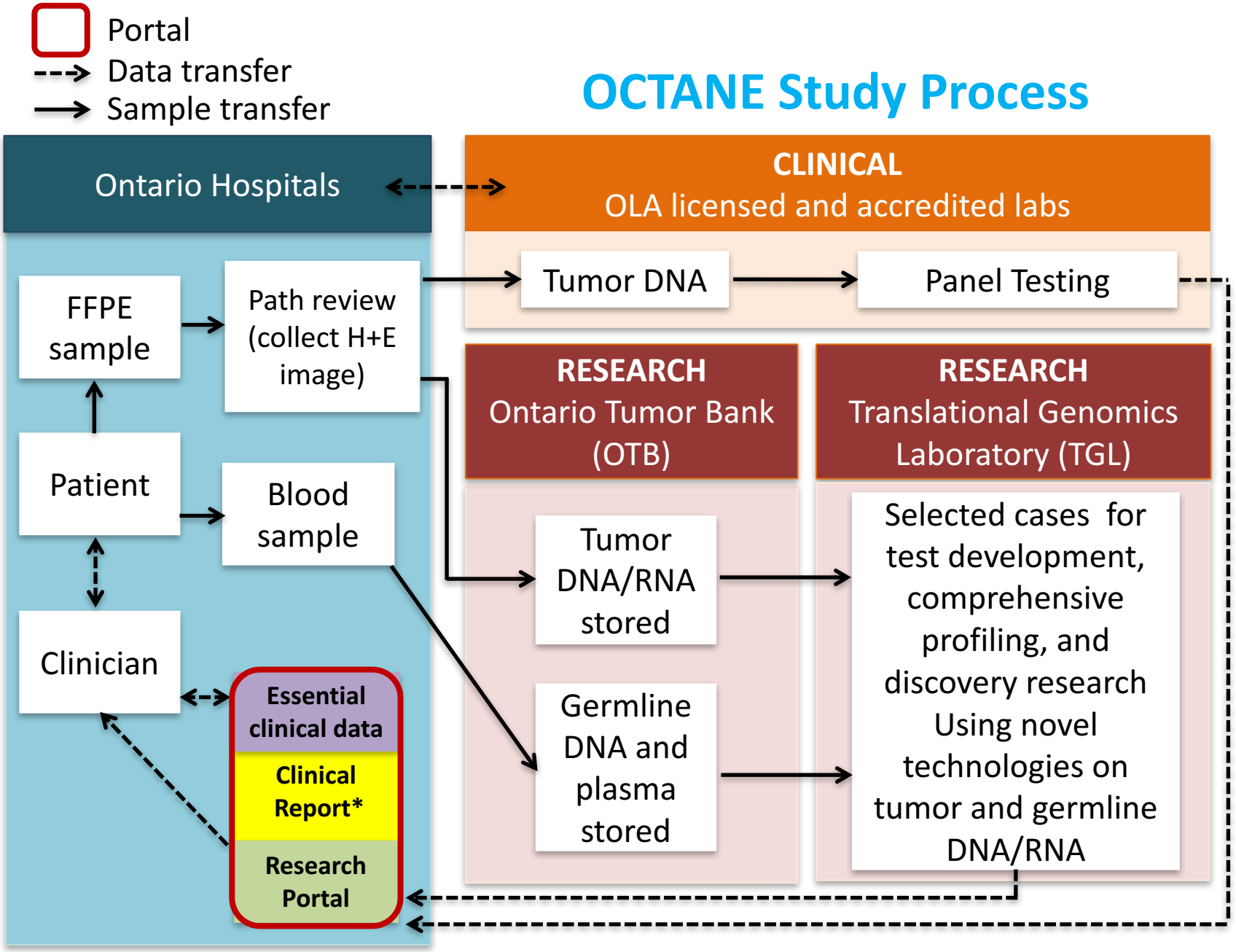
We are the **only** program of its kind in Canada that provides comprehensive molecular profiling of tumor specimens in a CAP-/CLIA-certified clinical laboratory.

IMPACT/COMPACT Accrual (Molecular Profiling Study at PM)



Stockley T, Bedard P et al. Genome Medicine 2016

CANCER GENOMICS PROGRAM



*Clinical report for lung, CRC, and melanoma patients only

Cancer Genomics Program (CGP)

Directors: Phil Bedard, Suzanne Kamel-Reid, Lillian Siu

2012

Launch of IMPACT/COMPACT molecular profiling initiative in PM

Support from PMCF and CCO's ACRU (Applied Cancer Research Units) Grant

2014

Became 1 of 8 founding members of AACR's GENIE data sharing project

Successful application in Genome Canada's GAPP grant

2016

Completed IMPACT/OCTANE – enrolled 3000+ pts

Launch of OCTANE (Ontario-wide targeted nucleic acid evaluation)

PM contributed 1,277 patient cases to AACR's GENIE (total of 19,000)

TGL (Translational Genomics Lab) created by PM and OICR

2017

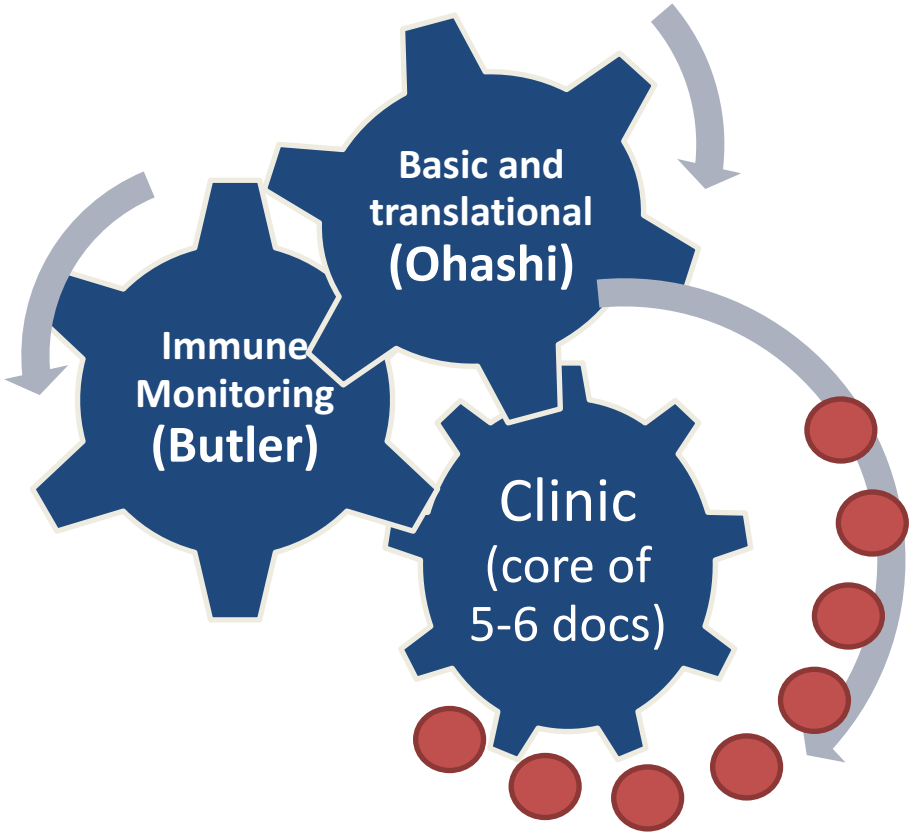
Launch of TF4CN (Terry Fox Comprehensive Cancer Centre Consortium Network)

One of the lead groups in CCTG's CAPTUR (Canadian profiling and targeted agent utilization trial)

Liquid biopsy program in planning

Tumor Immunotherapy Program (TIP)

Director: Pam Ohashi
Translational and Clinical Leads: Marc Butler, Lillian SIu



Cutting-edge research expertise spanning from basic immunology discoveries through clinical trials of immune therapies with a focus on improving our knowledge of the immune system to better diagnose, detect and target cancers

Sponsored clinical trials

- DDP-Phase I, II, III/multiple tumor types: Immune modulating agents (ICI, agonists), viruses, vaccines, CARs (Pharma)
- CTEP, Cancer Immunotherapy Trials Network [CITN] (US NCI)

Investigator Initiated Research

- Bench to Bedside – e.g. Adoptive Cell Therapy TILs (melanoma, ovarian, mesothelioma), TCR engineered cells, ACTIVATE
- Bedside to Bench – e.g. INSPIRE, META-DUR

Health services

- Quality of life evaluation (e.g. FACT-ICI)
- Tumor Immunotherapy Program Database

Discovery research

- SPECIAL, i-IMPACT, immune monitoring, identification of predictive biomarkers, PDX + TILs, work from many labs

Tumor Immunotherapy Program (TIP)

Directors: Pamela Ohashi, Marc Butler, Lillian Siu

2015

Launch of TIP

Creation of disease site champions to increase crosstalk between scientists and clinicians

Creation of TIP database

2016

Launch of INSPIRE and METADUR

Successful application of TFRI-sponsored iTNT (immunoTherapy NeTwork, supports ovarian cancer cohort of INSPIRE)

Successful application of TFRI-sponsored Program Project Grant (supports triple negative breast cancer cohort of INPSIRE)

First trial opened in Canada using TCR transduction technology

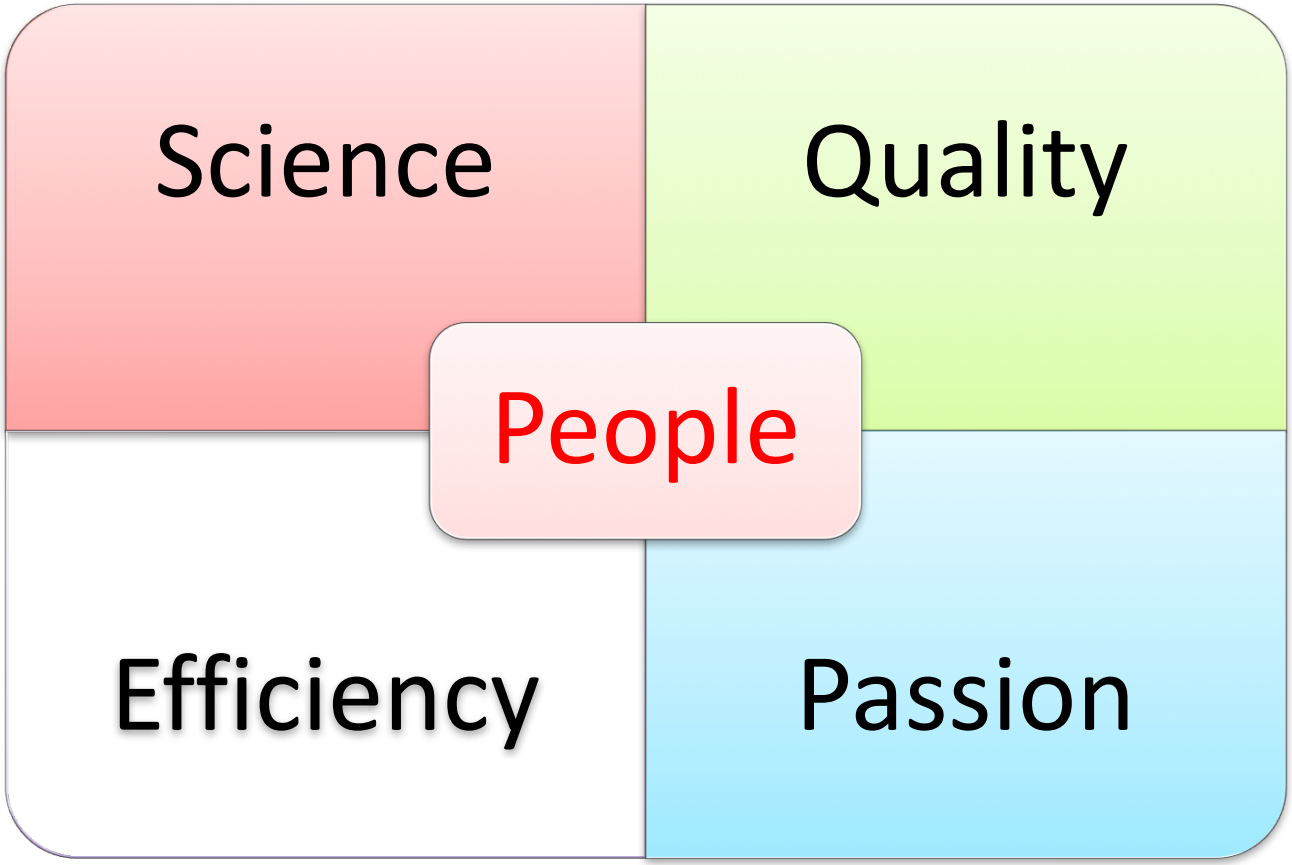
2017

TILs trial open in melanoma, ovarian cancer, mesothelioma. Head and neck target next site

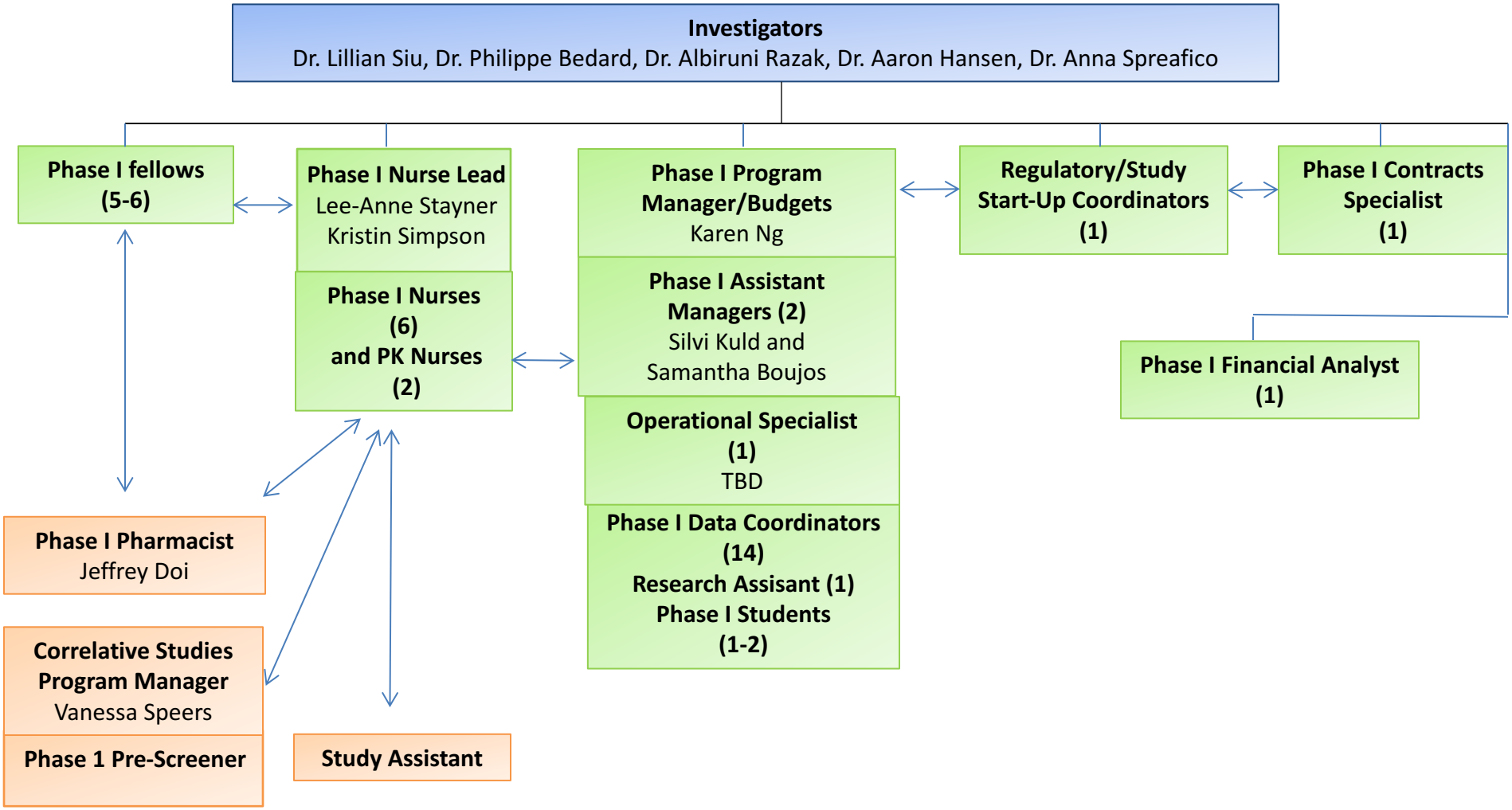
4 INSPIRE abstracts submitted to ASCO

Submission of OICR-TRI project proposal "Leveraging Vulnerabilities in Macromolecular Homeostasis as Therapeutic Targets in Ovarian Cancer" (Oza, Rottapel

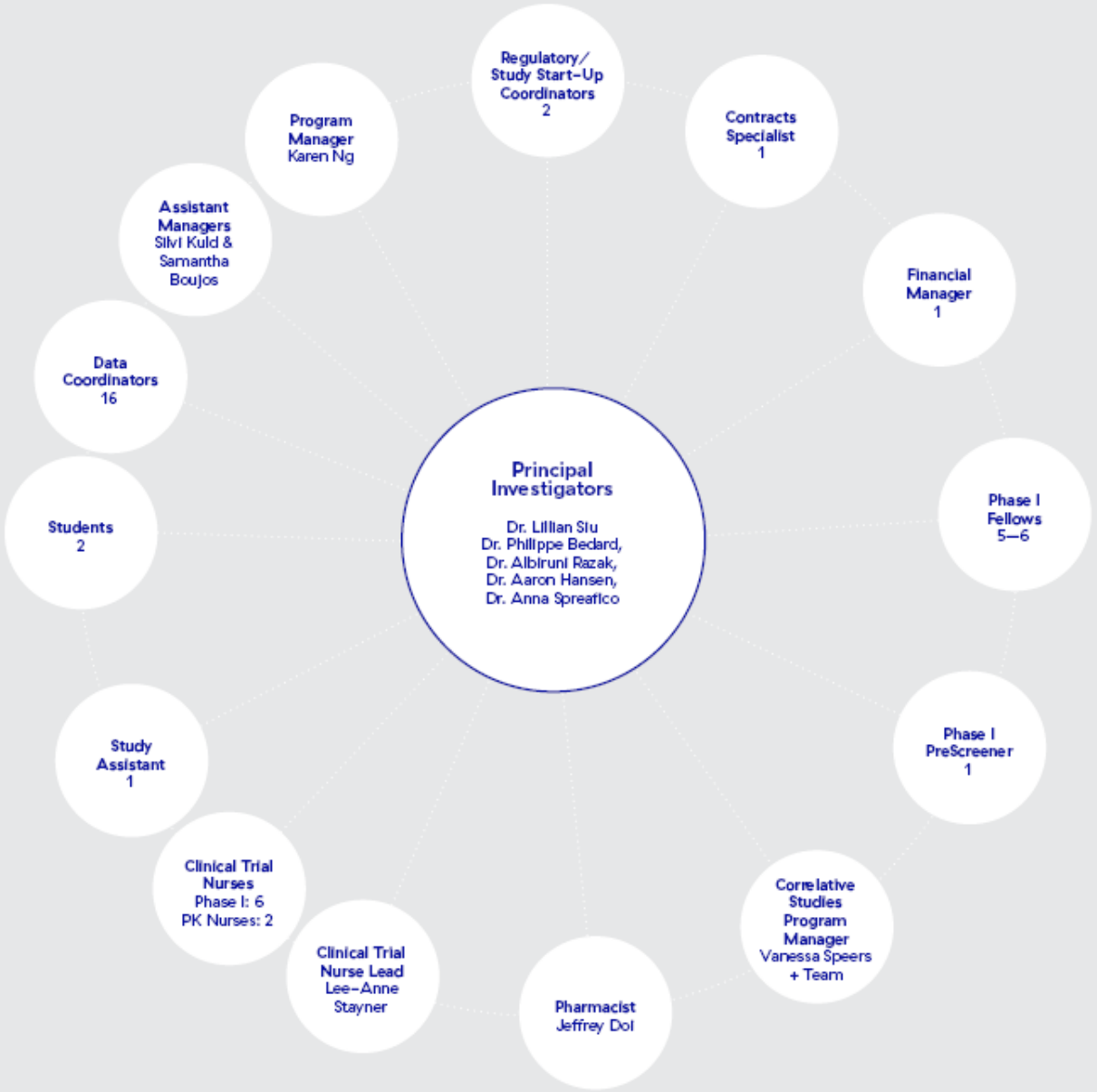
Building Bridges for Research: The Most Important Elements



Phase I Program Organizational Chart



The Phase I Team



Nursing Responsibilities

Protocol	Study Drug	Patient Care	Sponsor/Study Team
Protocol Review	Administration	Screening	Email communication – occurs daily with team
Investigator Meetings	Concomitant medications (interactions)	Baseline assessment	SAE reporting
Site Initiation Visits	Study drug diary	Evaluation and management of AEs	Teleconferences
Informed Consent	Attribution assessment (with PI oversight)	PK/PD	Weekly meetings with Phase 1 Team
Eligibility Criteria	Dose Modifications	Supportive care	
Registration			

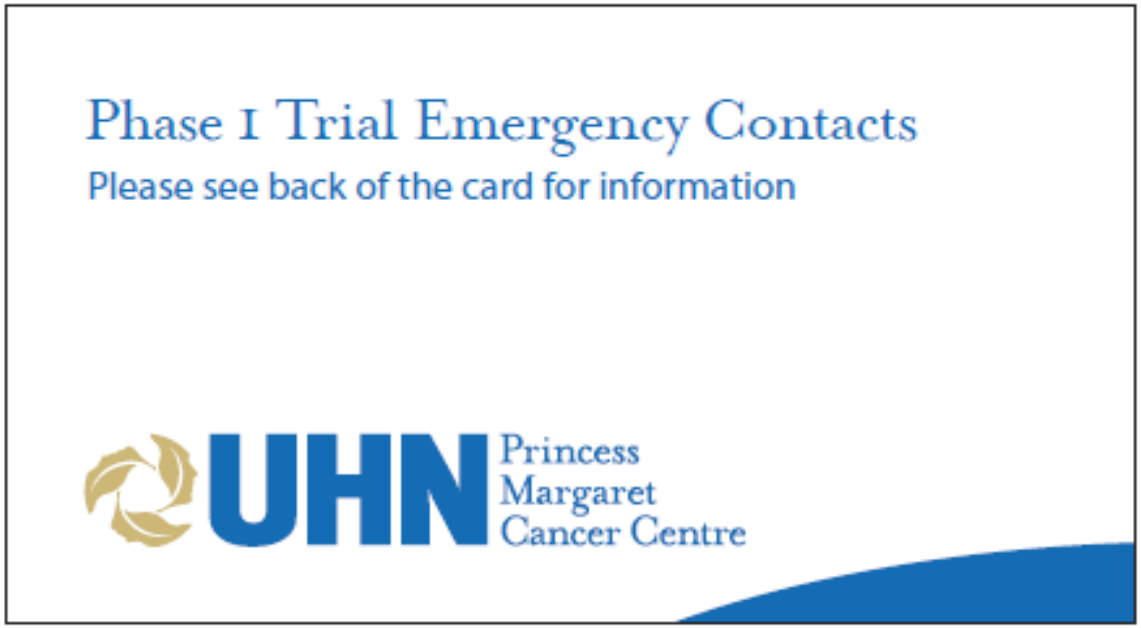
Phase I Fellowship Program

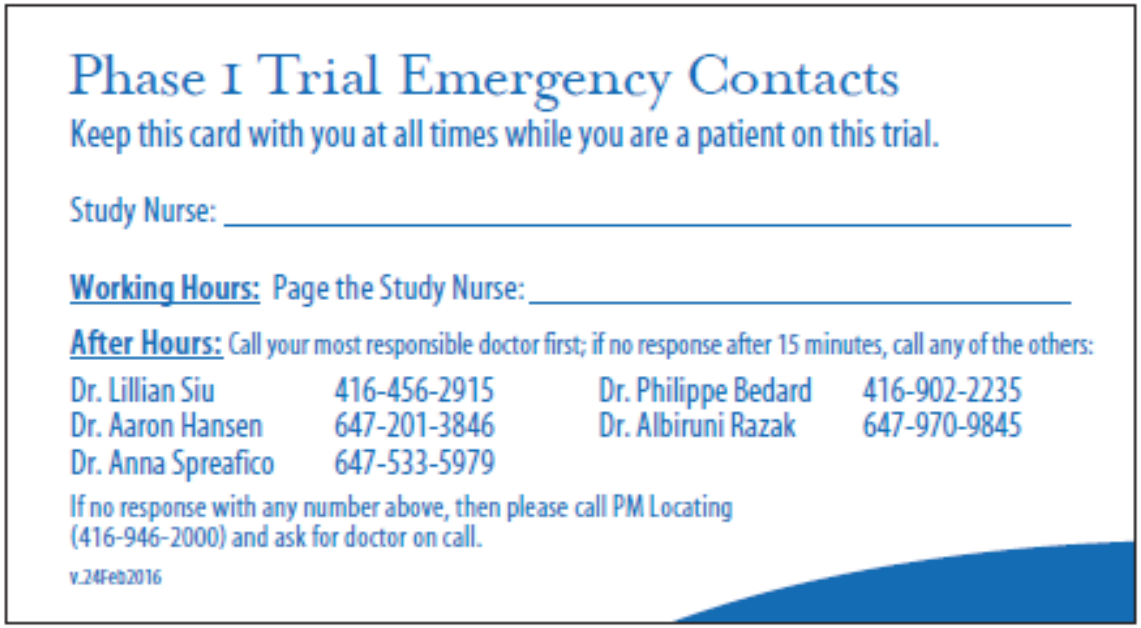
- The Phase I Fellowship Program is directed by Dr. Philippe Bedard and includes 4-8 clinical research fellows
- World class training program in experimental therapeutics and have consistently attracted trainees worldwide
- Two years of training in early Drug Development following their board certification
- There is a structured curriculum that includes active participation in the planning, coordination and implementation of selected phase I clinical trial protocols mounted

Fellowship Program

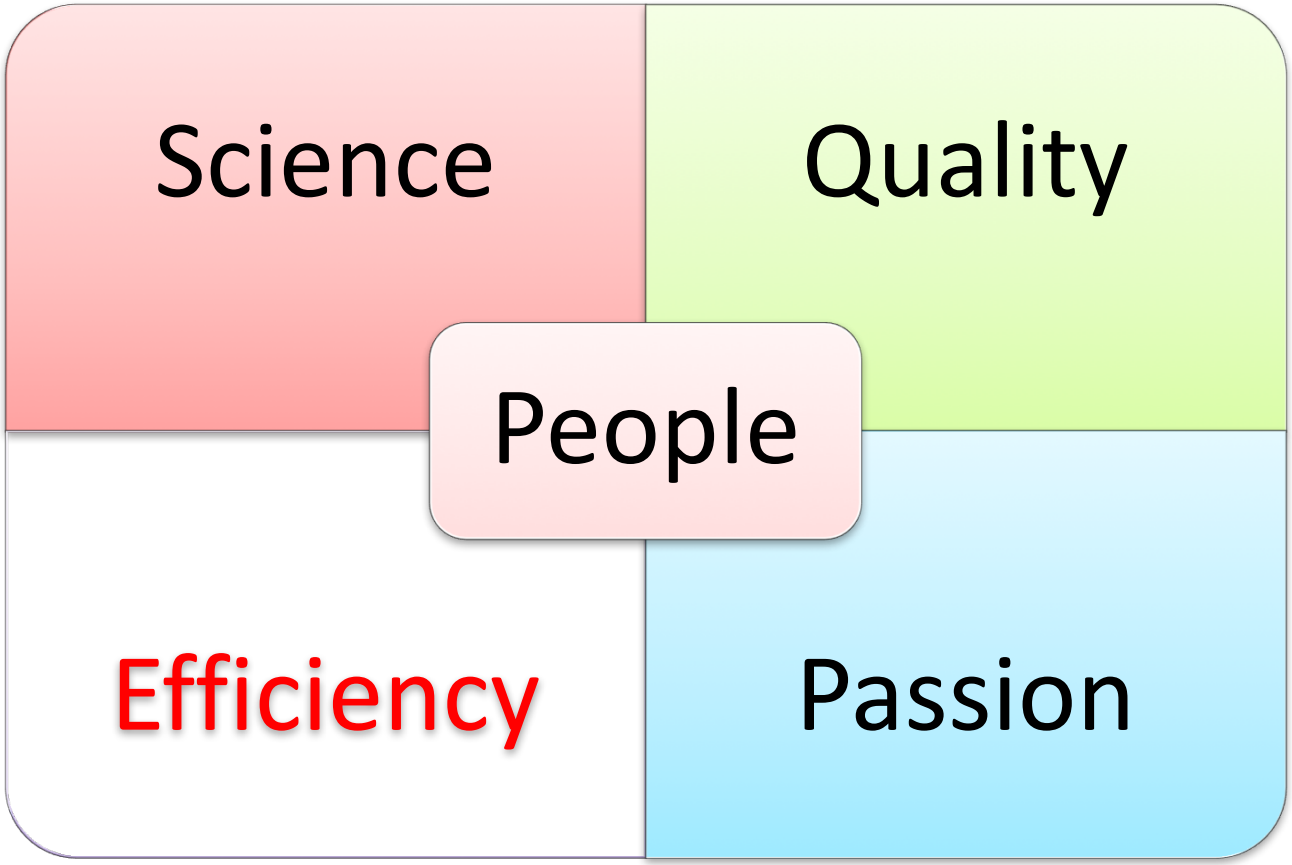
- **Responsibilities** – Phase I clinic, outpatient unit rostering, assigned to specific studies
- **Opportunities** – LOIs, protocol writing, day-to-day running of studies, teleconferences, investigator-initiated research projects with mentorship, presentations and manuscript writing
- **Education** – Journal club, weekly teaching sessions (together with departmental fellows)

Phase 1 Wallet Card





Building Bridges for Research: The Most Important Elements



What works well?

- SIV – not required to wait for REB and contract/budget approval
- Staff Documents (CVs, MLs) – maintained by administrative staff
- Flow of information - data coordinators involved in decisions, weekly Phase 1 team meetings
- Templates – emails, source documents, training records, deviation reporting
- Standardized Trackers – consent, patients, protocol versions, and other regulatory documents
- IRB/REB – knowledgeable, quick turnaround, accessible
- Back-up – coordinators with access to study documents and eCRFs to allow for absence coverage and quick assistance during period of heavy data volumes
- Shared Drive – electronic study files organized and filed in the same manner on a shared space
- Administrative Database – easy reference to current protocol and consent forms for clinic staff (paperless)

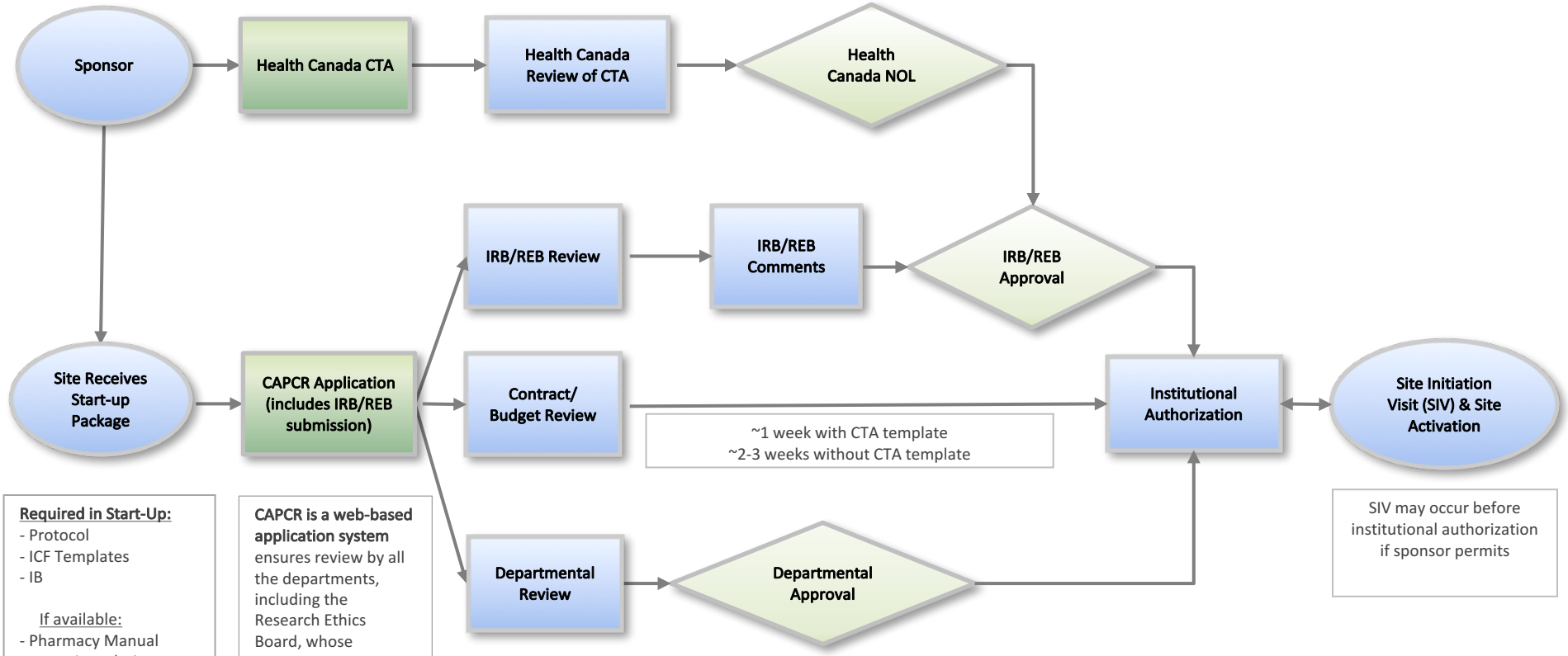
Submission Flow Process for Phase I, Princess Margaret Cancer Centre

Health Canada Clinical Trial Application (CTA) is submitted by the sponsor.

The **Health Canada No Objection Letter (NOL)** is required before REB Approval can be granted.

IRB/REB Full Board Meetings:
- Occur **once a month,** typically on the last Friday of each month
- Submission deadline (via CAPCR) is **2 weeks** before the IRB/REB Meeting date (typically at 12pm on the second Friday of each month)

IRB/REB Comments are responded to in the form of a letter, and the sponsor may be involved to assist with questions. ICF revisions based on comments are sent to the sponsor for approval, and the approved ICF is sent with the response letter to the IRB/REB.



SIV may occur before institutional authorization if sponsor permits

Required in Start-Up:
- Protocol
- ICF Templates
- IB

If available:
- Pharmacy Manual
- Procedures/Lab
- Manual
- Imaging Manual
- Questionnaires
- Other materials as applicable

Not Required:
Patient Wallet Card (standard Phase I Emergency wallet card used instead)

CAPCR is a web-based application system ensures review by all the departments, including the Research Ethics Board, whose approval is required before study initiation.

The regulatory submissions coordinator is responsible for initial application submission for study start-up.

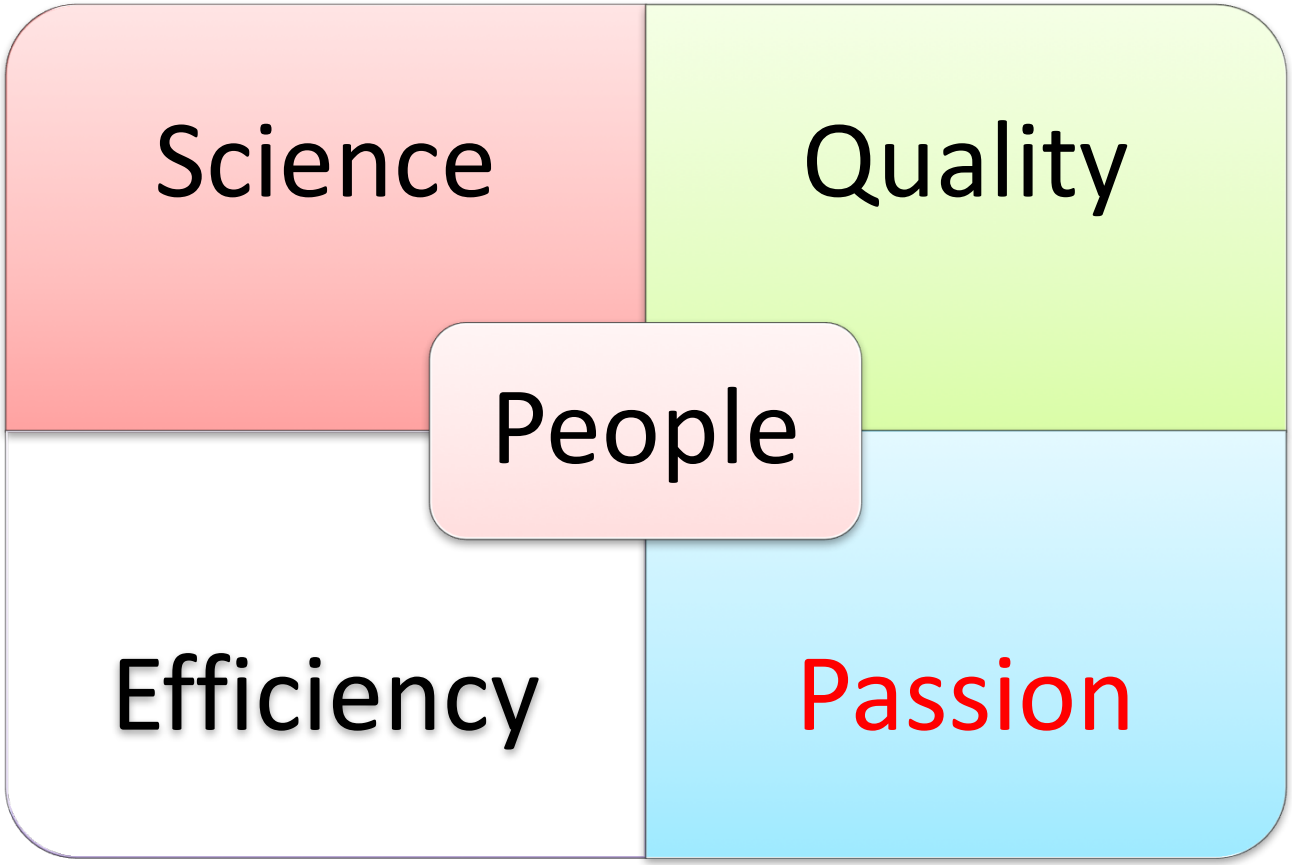
Timeline from submission to approval:
8 – 12 weeks depending on responses from PI or sponsor

Role of the Phase I Financial Analyst

- Start-Up
- Patient Visits
- Invoiceables
- Close-Up costs

- Financial Operations of the Trial
  - Negotiate the budget with Sponsor
  - Ensure correct payments from Sponsor
  - Liaise with Sponsor on Financial matters
  - Liaise with Internal Accounts Receivable and Accounts Payable
  - Estimate the Profit and Loss for the each Investigator and for the Program

Building Bridges for Research: The Most Important Elements



Lessons from “Good to Great”

1. Level 5 Executive Leadership

- Workmanlike diligence – more plow horse, than show horse.
- Ambitious for the program, not themselves

2. First Who, Then What

- Get the right people on the bus; get the wrong people off the bus
- Put your best people on your biggest opportunities, not the biggest problems

3. Confront the Brutal Facts (But Never Lose Faith in the Potential for Greatness)

- Impossible to make good decisions without an honest confrontation of the brutal facts. Create a culture wherein the truth can be heard
- Don't waste time trying to "motivate people". The right people are self-motivated but can be de-motivated

4. The Hedgehog Concept

- Organizations should only do what they 1) can be great at, 2) can make money [or be successful] at and 3) have a passion for doing
- Hedgehog programs are simple creatures that know one big thing and stick to it. Other programs are more like foxes that know many things but lack consistency

Examples from Phase I Program

- It's all about the people – they must share the same passion
- Communication, communication, communication:
  - Weekly face-to face meeting
  - Daily sign outs from fellows (all copied)
  - Weekly staff review of patients (CT scans, bloodwork, etc) starting treatment
  - Good and poor practices are discussed
- Annual retreat to propose actionable improvements to the program
- Regular team building events
- Hedgehog concept: Conducting high quality phase I study with appropriate patients, reliable assessments, compliance to protocol, strong and on-time data management, engaging physicians – This is not a strategy or a vision – it is an understanding

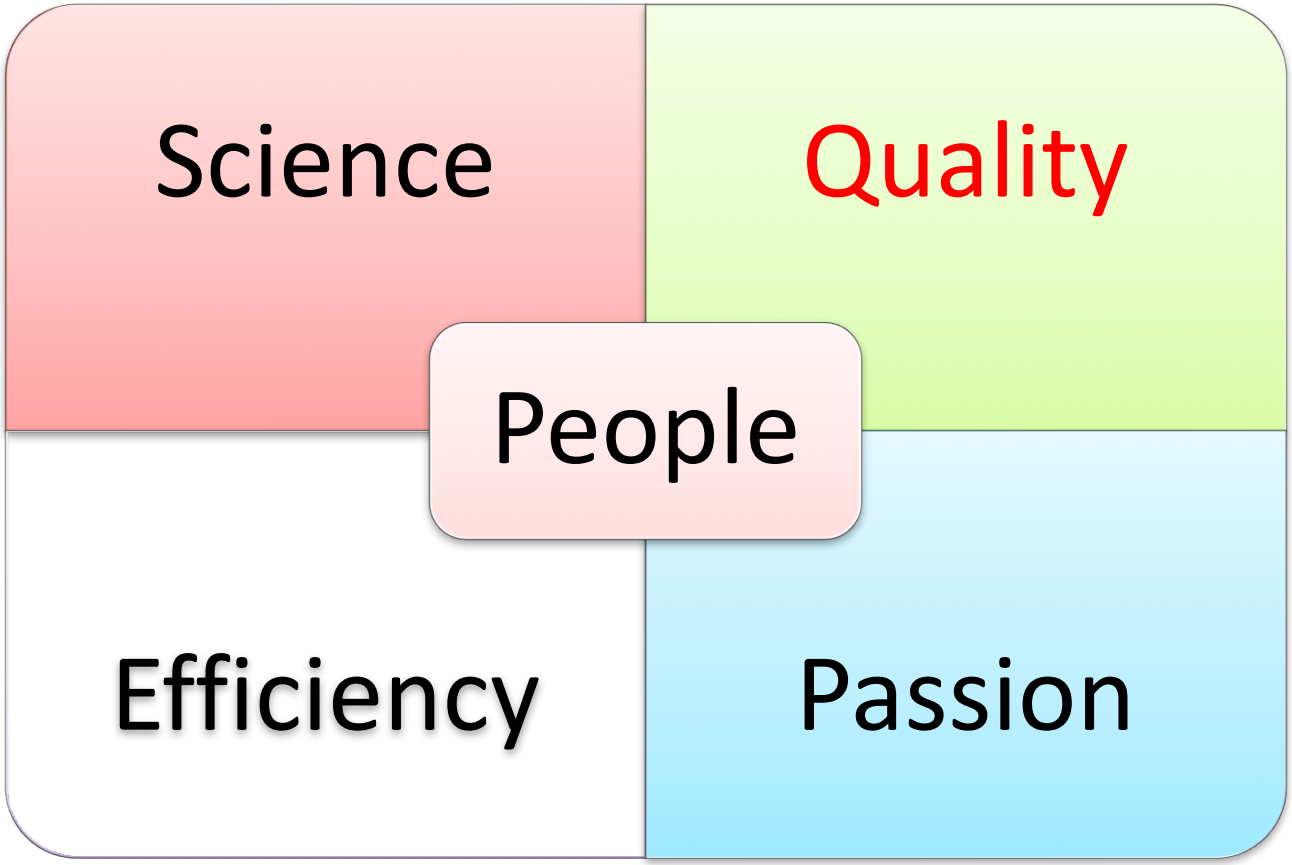
Phase I Retreat – New Ideas Come

Group	Ideas
Data Coordinators	• PK signing binder • Urgent tumor measurement bookings • Follow-up visit compliance
Pharmacy	• Pharmacy notification for new patients starting trial – ensure drug availability
Start up	• Budget and contract tracker
Trial Nurses	• Research charts – sign out sheet • Patient self-check in Patient flow board
Fellows	• Automated adverse event grading • Updated phase I list for public access • Drop box for photos
PIs	• Patient satisfaction survey • Improvements for patient waiting experience • Platinum pin for patient appreciation

Examples from CGP and TIP

- Engaging multiple research groups with complementary and in some cases competing interests – need everyone to see the value to work together 'for the bigger common good'
- Vision and mission, short term and long term goals, benchmarking against other world-class programs
- Sentinel projects (e.g. IMPACT/COMPACT for CGP, INSPIRE and METADUR for TIP) – team building, conflict resolution, trouble shooting, success sharing
- Regular meetings with executive committee, key operational team, to discuss programmatic issues
- Transparency is key including financial matters
- Constantly seek out peer-reviewed funding opportunities
- Opportunities for young investigators and scientists

Building Bridges for Research: The Most Important Elements



US National Cancer Institute Phase I UM1 Grant

- (PI: **L. Siu, A. Oza, D. Sullivan [Moffitt]**; Phase I UM1 grant)
  - Membership to NCI Experimental Therapeutics Clinical Trials Network (ETCTN)
  - Access to NCI-IND agents in high priority areas of unmet medical need
  - Integrate molecular characterization, pharmacology, cancer biology & imaging into trials

Preferred Partnerships with Many Pharmaceutical Partners

Examples:

- **Genentech/Roche:** The only Canadian Core Immuno-Therapy (imCORE) site, rest in US, EU and Asia (total of 21)
- **Novartis:** Long standing preferred partner – majority of Novartis FIH trials are open at PM
- **Bristol-Myers Squibb:** PM is a Centre of Excellence, involves in its IO ”Surges”
- **GSK:** One of 6 Oncology Clinical and Translational Consortium members (OCTC) worldwide

Preferred Partnerships with Many Pharmaceutical Partners

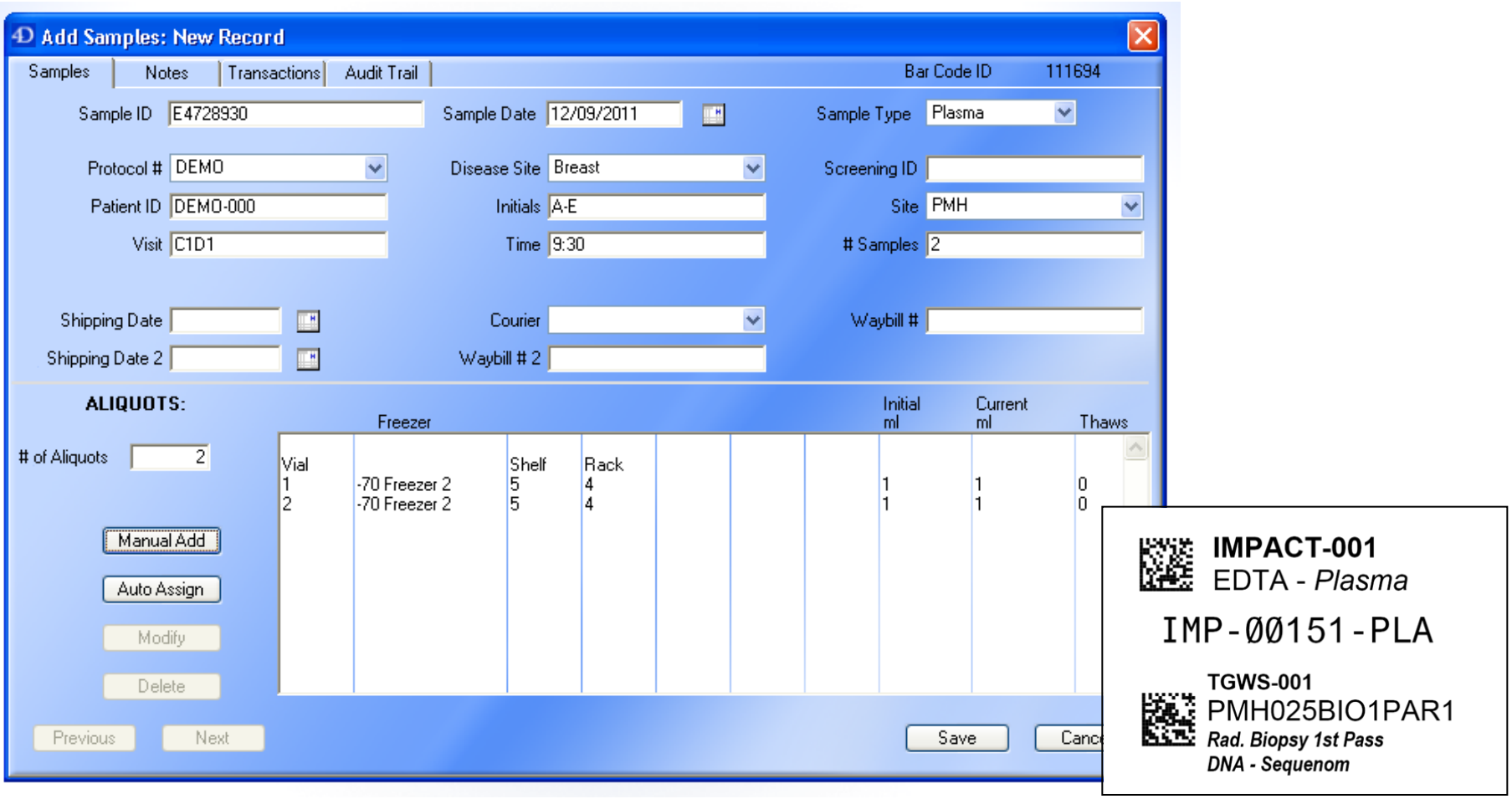
What does a formal alliance Involve and mean?

- Alliance relationship specialist role
- Master confidentiality disclosure agreement (CDA) in place
- Master study agreement (contract) in place – only need to negotiate study-specific budget
- Regular teleconferences between sponsor, core alliance physicians, alliance relationship specialist
- Face-to-face meetings at AACR, ASCO, special summits to promote interactions and collaborations between alliance sites
- Regular pipeline webinars to highlight the science and non-clinical data for novel compounds entering (so soon to enter) clinic

Location, Location, Location – Central on Clinical Trials Short Stay Unit

Biospecimen Database

Software package the focuses on freezer inventory, sample labeling, tracking, and sample and data management for laboratories and biorepositories.



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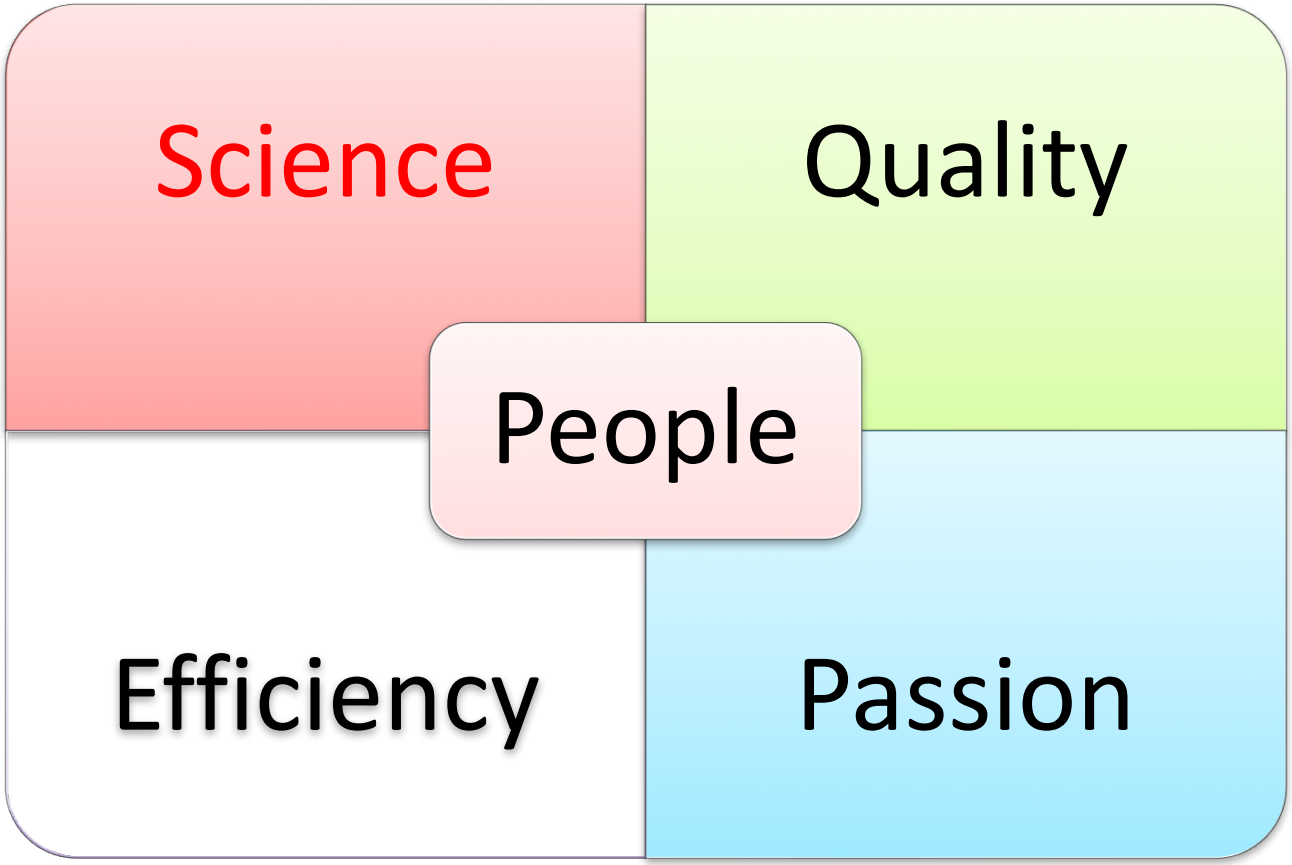
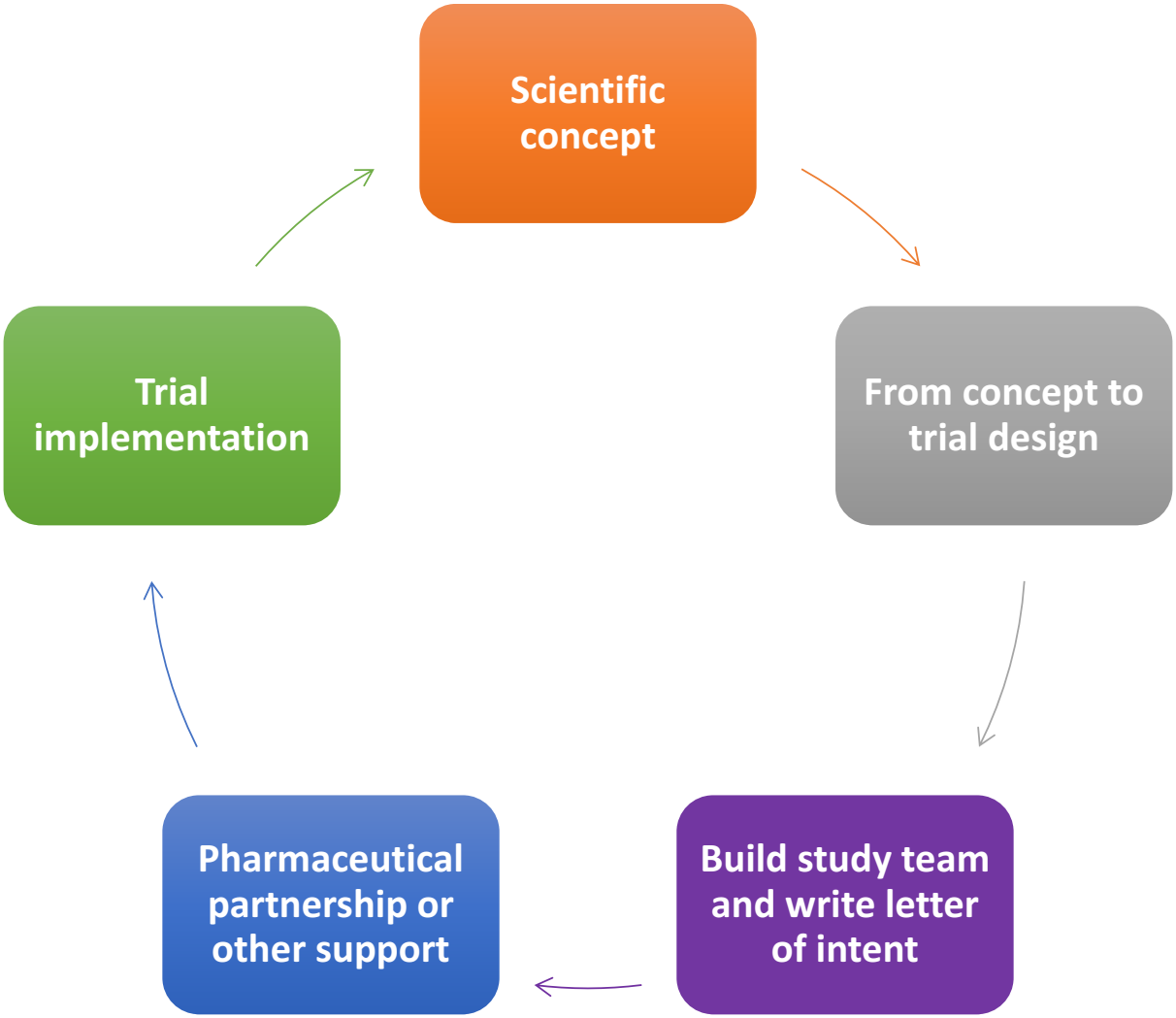
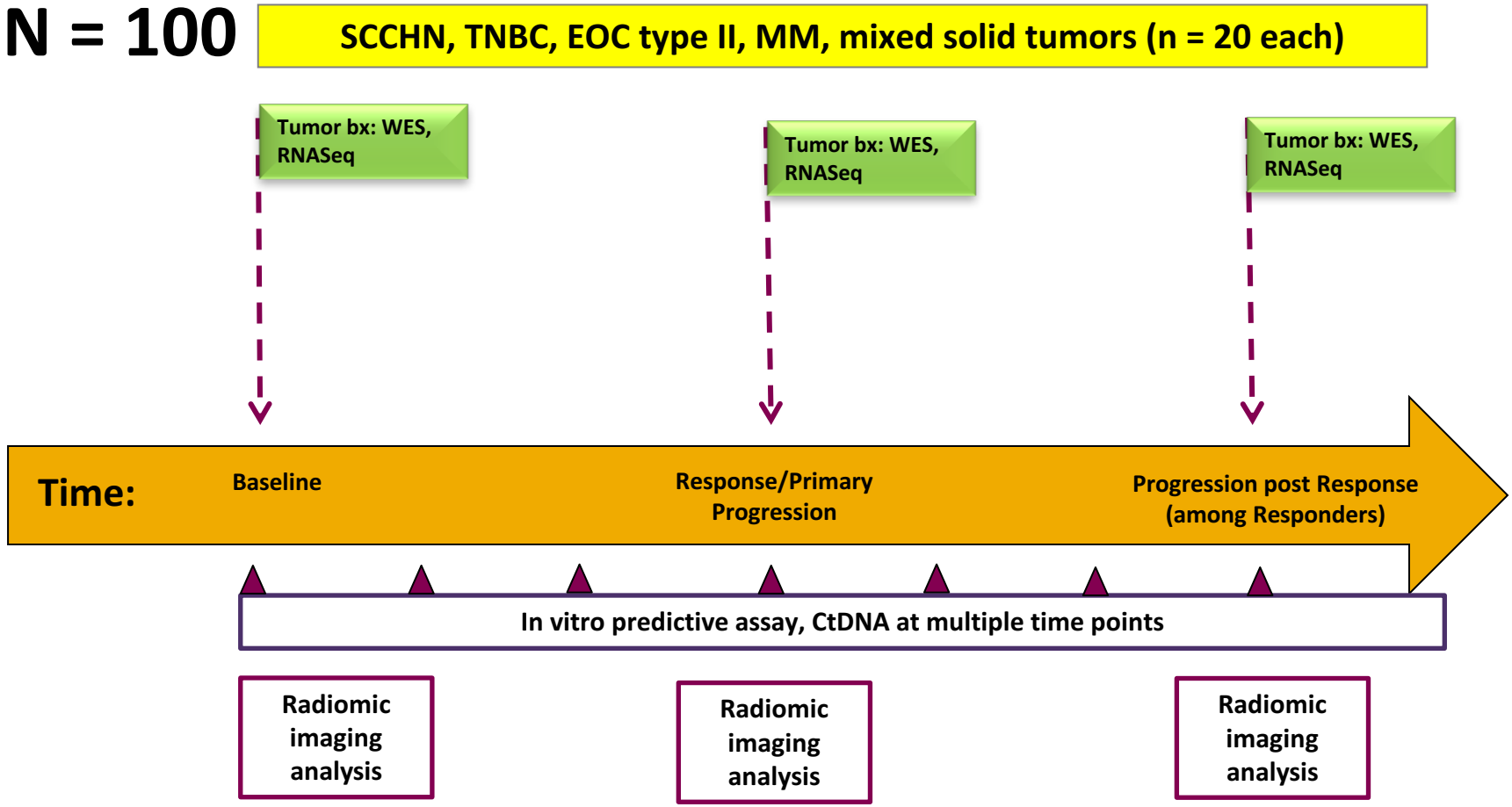


How to bring a concept from bench to bedside (investigator-initiated research)?



INvestigator-initiated Phase II Study of Pembrolizumab Immunological Response Evaluation (INSPIRE)

NCT02644369



What Metrics are Important?

- Efficiency
- Quality of work:
  - Data quality – accurate and on time
  - Lack of protocol deviation and violations
  - Meeting deadlines
  - Outstanding care and follow up of patients
  - Professionalism and attitude of team
- Accrual
- Scientific input and engagement
- Cost

Acknowledgements

- All internal and external partners
- Bras Drug Development Program
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- Ontario Institute for Cancer Research
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- Terry Fox Research Institute
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