CLINICAL TRIALS:
MYTHS, REALITIES, AND THE UNSPOKEN BENEFITS

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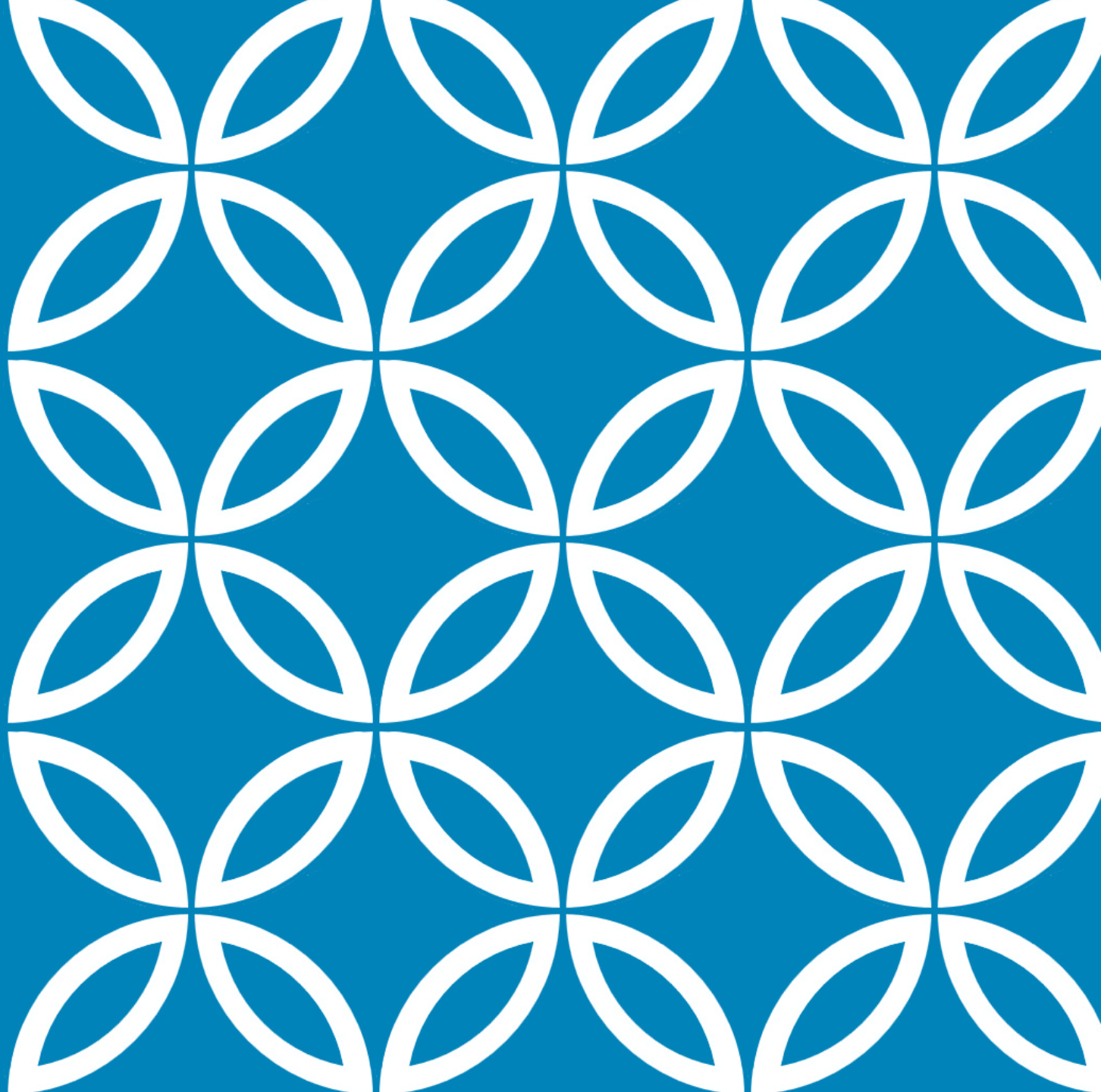
OUTLINE

1. What is a Clinical Trial (and what is it not)
2. The unspoken benefits of clinical trials
3. Is a clinical trial available to you?



BASIC DEFINITIONS TO SET THE STAGE

- Clinical Trial
  - A Clinical Trial is a **controlled** experiment involving an **intervention** in a defined **population,** for the purpose of determining if the intervention is **safe** and/or **effective**
    - Controlled
    - Intervention
    - Defined Population
    - Safety and Efficacy
- Drug Development
  - **the entire process of drug discovery and clinical testing of novel drug candidates, including pre-clinical studies, "first-in-human" studies, and the four phases of clinical trials**

WHY DO WE DO CANCER CLINICAL TRIALS???

MYTH #1:

- so greedy Big Pharma can develop a drug to make money
  - Only 3.4% of oncology drug candidates successfully receive regulatory approval[1]
  - The cost of developing an anticancer drug varies from 1 – 4 billion dollars[2]

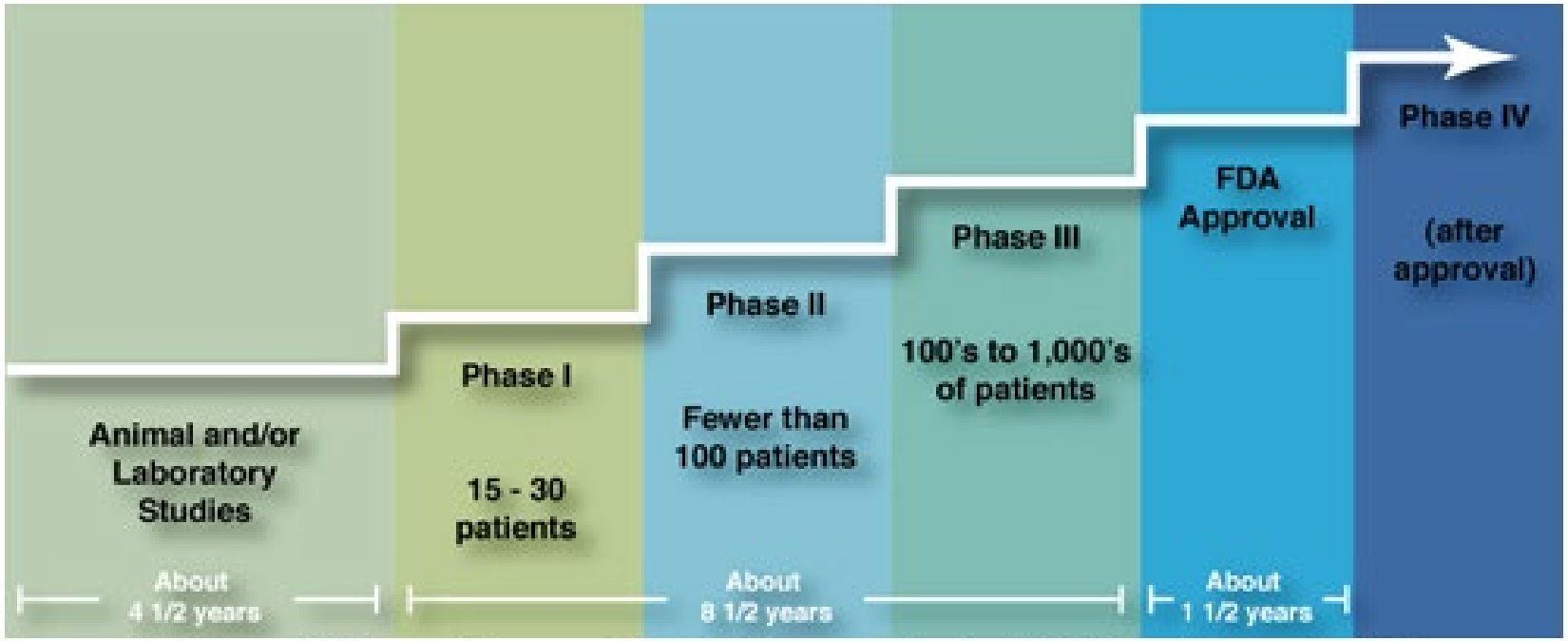
REALITY #1:

- So we can make treatments that are more effective
- So we can make treatments that are safer
- So we can make treatments that are less expensive
- So we can improve quality of life

1. Wong, Biostatistics 2019 2. Schlander, PharmacoEconomics 2021

CLINICAL DRUG DEVELOPMENT

- 'phases' of clinical trials

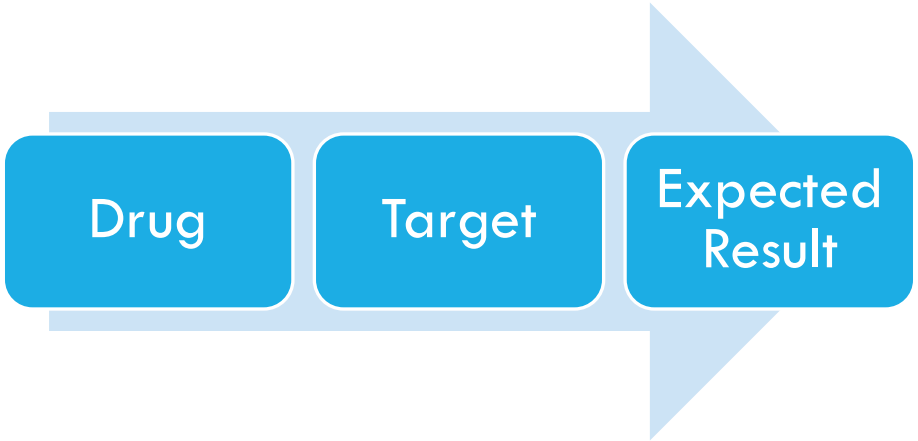


The Drug and Approval Process in the 1990s as reported by the National Cancer Institute.

PRECLINICAL EXAMPLE - RITUXIMAB

B cell lymphocytes have a protein on their surface called CD20

- Biogen Idec engineered a monoclonal antibody that specifically binds to CD20
- Pre-clinical studies in monkeys showed that when they were injected with the anti-CD20 monoclonal antibody, their B lymphocytes were depleted



PHASE I – DETERMINE SAFETY

Goal: find the safest dose of a new drug without harmful side effects.

- **Maximum Tolerated Dose (MTD) or Recommended Phase 2 Dose (RP2D)**

usually include 15 to 30 people. Usually patients are relapsed/refractory and have no other reasonable option

Inclusion criteria is often broad – eg multiple histologies

Typically, treat patients in **cohorts** – usually 3 patients at a time

- first cohort receives a low dose of the new drug.
- If no severe side effects occur, then a new cohort receives a higher dose of the same drug.
- The dose increases with each new cohort until the researchers see too many side effects
  - The **MTD** is usually one dose below this final cohort

PHASE I EXAMPLE - RITUXIMAB

In 1994 Dan Maloney from Stanford performed a dose escalation study in 15 patients with relapsed indolent B cell lymphoma.

5 dose levels were tested: 10, 50, 100, 250, and 500mg/m2

3 patients were treated with a single dose at each dose level. There was no significant toxicity at any dose level. Based on PK data, 375mg/m2 was chosen as the dose to test further in Phase 2

6 of 15 patients had reduction in the size of their lymphoma

The side effect profile included fevers, nausea, low blood pressure and bronchospasm

Maloney et al, Blood 1994

PHASE II – ESTIMATE EFFICACY

Goal – how well does the drug work in a certain disease

Usually less than 100 patients, usually relapsed

A better chance to estimate side effects in a larger number of patients, at the planned treatment dose

If the treatment seems successful in Phase 2 (the **outcome of interest**), the effort and expense of a Phase 3 trial may be justified

Drugs are not usually approved based on Phase 2 studies, but sometimes they receive Accelerated Approval (US) or Notice of Compliance with Conditions – NOC-C (Canada)

PHASE II EXAMPLE - RITUXIMAB

In 1998 Peter McLaughlin from MD Anderson published a Phase 2 study in 166 patients with relapsed or refractory follicular lymphoma.

The dose was 375 mg/m2 weekly x 4 weeks

Overall response rate was 74%, with complete response in 50%, and median progression free survival of 2 years.

Most side effects occurred with the first infusion, most were grade 1 or 2 and the most common were fever and chills. Only 12% of patients had grade 3 or 4 toxicity

This trial resulted in FDA accelerated approval of rituximab for relapsed follicular lymphoma in 1997

Maloney et al, Blood 1994

PHASE III – **PROVE** IT WORKS BETTER

Goal -- compare the new treatment with the standard treatment.

Phase III trials may include **hundreds** to **thousands** of patients.

In general, each patient enrolled in a Phase III clinical trial has an equal chance of participating in one of two or more **arms** (groups) of the study **(randomization)**.

In a clinical trial with two arms:

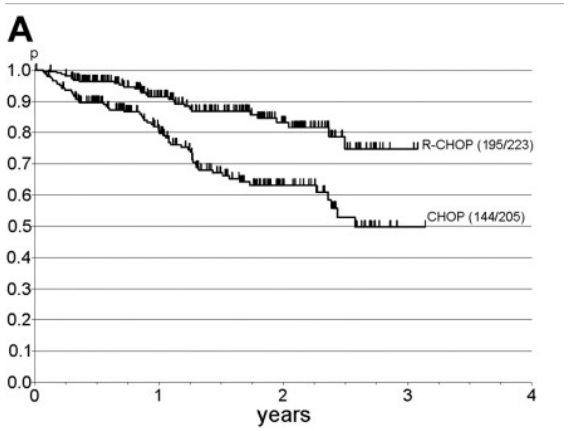
- The **control group** receives the standard treatment
- The **investigational or experimental group** receives the new treatment being tested

PHASE III EXAMPLE - RITUXIMAB

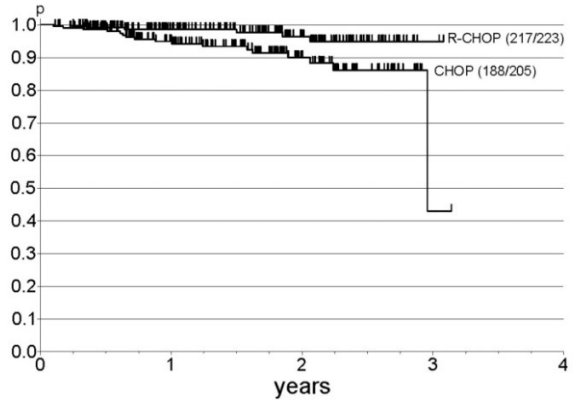
In 2005 the German Low Grade Lymphoma Study Group (GLSG) published a phase 3 study of CHOP versus CHOP plus Rituximab

428 patients with previously untreated Follicular Lymphoma were randomized to CHOP or R-CHOP

- ORR was higher with RCHOP (96 vs 90%)
- Time to treatment failure was better with RCHOP



Overall Survival was better with RCHOP



Maloney et al, Blood 1994

HOW HAS RITUXIMAB AFFECTED FL OUTCOMES

2004: treatment for patients diagnosed with FL in 1994 resulted in an average overall survival of 7-10 years

2005: RCVP versus CVP – average length of remission was 34 vs 15 months (untreated)

2006: maintenance Rituximab versus observation for relapsed FL: average length of remission was 51 months versus 15 months

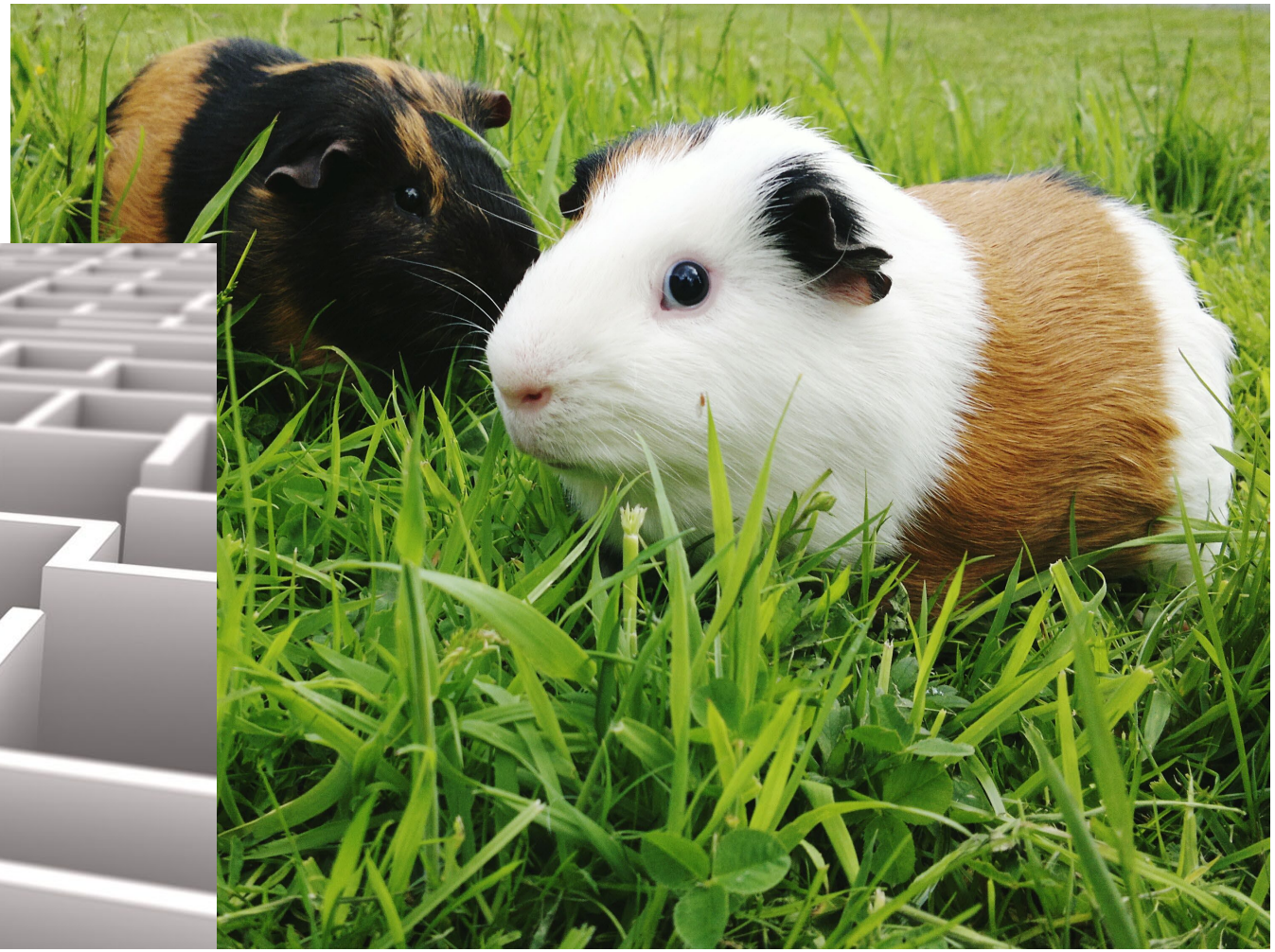
2011: maintenance Rituximab versus observation for untreated FL: average length of remission was 10.4 years versus 4.1 years

Average survival if diagnosed in 1994: 7-10 years

Average survival if diagnosed in 2014: at least 25 years

1000's of patients were able to access Rituximab through clinical trials before it was available for routine care

MYTH #2: LAB RATS AND GUINEA PIGS



REALITY #2 – THE REQUIRED STEPS FOR A CLINICAL TRIAL

- STUDY DESIGN:
  - Sponsor (Pharma company or Cooperative Group or Individual) writes the trial protocol
    - Every element of the design needs to be ethically justified
    - Usually written by a committee of experts
    - Publicly funded studies now require patient representation on the protocol design committee
  - Sponsor submits the protocol to regulatory body (FDA and/or Health Canada) for ethical and safety review
  - Once approved by FDA/HC, every protocol must be submitted to one or more Research Ethics Board(s) – REB
    - REB uses ethical framework to review the protocol and ensure that **potential gains outweigh potential harms**

The Ethical Framework: Good Clinical Practice (GCP)
PROTECTION OF THE STUDY PARTICIPANT

- The Sponsor has a responsibility to Monitor/Audit studies in progress
- The regulators (HC/FDA) have an Audit and Monitoring program in place
  - They can and do conduct random and for-cause inspections / audits

MYTH 2: “PLACEBOS ARE UNETHICAL”

REALITY 2: ETHICAL PLACEBOS

Randomizing to an active treatment versus a placebo is unethical

However, there are trial designs where placebos are ethical:

- A Phase 3 trial of (Standard plus Experimental) versus (Standard plus Placebo)

STEPS TO PARTICIPATE IN A CLINICAL TRIAL

INTRODUCTION TO THE TRIAL, THE STUDY COORDINATOR, AND THE ICF

- You have a condition that needs treatment
- Your doctor says there is a clinical trial that you **might** be eligible for
- Your doctor explains what the standard treatment would be, and how the trial is different
- Your doctor explains why you think the experimental treatment **might** be better
- You say you **might** be interested
- Your doctor introduces you to the Study Coordinator. You ask any questions you may have at this point
- Your are given the Informed Consent Form to take home and read, and arrangement is made for the next contact

STEPS TO PARTICIPATE IN A CLINICAL TRIAL

THE INFORMED CONSENT PROCESS

- You return after having reviewed the ICF and thought about it
  - If not interested, you inform your doctor. Don't be afraid to explain why. If your doctor thinks you have misunderstood something that materially affected your decision, they may provide you with the correct information. Your doctor will respect your decision and will not let it affect the quality of care you receive
  - If interested, make sure that all questions you have get answered
- You sign the ICF in the presence of the doctor or study coordinator, and then officially enter **Screening**

STEPS TO PARTICIPATE IN A CLINICAL TRIAL

THE SCREENING PROCESS

- During screening, your doctor will use strict criteria to ensure you meet the **eligibility criteria**
- Several tests will be required. Some will already have been done as **standard of care.** Some will need to be done now as **study specific interventions.** Some testing you already had done might need to be repeated if they were done **outside of window**.
- Once testing is complete, your doctor will confirm that you meet all of the **eligibility** criteria and none of the **exclusion** criteria
- You will then have a **screening visit** during which your doctor will double check your symptoms and perform physical exam.
- During or after the screening visit, you will be either **excluded ("screen failed"), randomized, or registered** (if it is a non-randomized study)

- Then, your treatment on the study begins!

STEPS TO PARTICIPATE IN A CLINICAL TRIAL

THE ON-TREATMENT EVENTS

- You will have a schedule of events, that includes
  - All required study visits
  - All required study tests – blood, urine, imaging, EKG, etc
  - All required quality of life / patient-reported outcomes
- At each visit, you can expect a thorough review of all of your symptoms, and a physical exam
  - Old problems will be reviewed to see if they have changed in grade/severity – example arthritis that changes from grade 2 at baseline to grade 3 while on study will be counted as an adverse event
  - All new problems will be reviewed, categorized, graded, and your doctor will decide if they are related or unrelated to study treatment. – example – if you are in a car accident while on study and you were the passenger, this will be recorded as an adverse event that is unrelated to study treatment. But if you are the driver, your doctor might decide it is related to treatment.
- The assessment of response will be according to the study protocol
  - Investigator reviewed versus Independent Response Assessments

Q&A #1

Fatigue is one of the suite of adverse effects doctors evaluate during clinical trials. What fatigue assessment does Dr. Macdonald use?

Fatigue Scores:

ECOG Performance Status:

- 0 = normal energy level
- 1 = reduced energy, but able to carry out normal tasks
- 2 = must rest <50% of daytime
- 3 = spends >50% of daytime resting
- 4 = bedridden

CTCAE:

Navigational Note: -					
Fatigue	Fatigue relieved by rest	Fatigue not relieved by rest; limiting instrumental ADL	Fatigue not relieved by rest, limiting self care ADL	-	-
Definition: A disorder characterized by a state of generalized weakness with a pronounced inability to summon sufficient energy to accomplish daily activities.					
Navigational Note: -					

KARNOFSKY PERFORMANCE STATUS SCALE DEFINITIONS RATING (%) CRITERIA

Able to carry on normal activity and to work; no special care needed.	100	Normal no complaints; no evidence of disease.
	90	Able to carry on normal activity; minor signs or symptoms of disease.
	80	Normal activity with effort; some signs or symptoms of disease.
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed.	70	Cares for self; unable to carry on normal activity or to do active work.
	60	Requires occasional assistance, but is able to care for most of his personal needs.
	50	Requires considerable assistance and frequent medical care.
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly.	40	Disable; requires special care and assistance.
	30	Severely disabled; hospital admission is indicated although death not imminent.
	20	Very sick; hospital admission necessary; active supportive treatment necessary.
	10	Moribund; fatal processes progressing rapidly.
	0	Dead

ASSESSING ADVERSE EVENTS IN CLINICAL TRIALS

When interpreting and comparing different clinical trials, it is important to know that the trial reports use the same meaning when reporting toxicity

- example – patient on clinical trial is admitted to hospital with fever, nausea, diarrhea and low blood pressure. If one trial calls this vgastroenteritis and another trial calls this flu and yet another calls this sepsis or hypotension, then you cannot compare the side effects of drug a versus drug b

- we also need a standardized way to Grade the severity of a side effect

We use the Common Terminology Criteria for Adverse Events (CTCAE)

Common Terminology Criteria for Adverse Events (CTCAE) v5.0

Publish Date: November 27, 2017

Introduction
The NCI Common Terminology Criteria for Adverse Events is a descriptive terminology which can be utilized for Adverse Event (AE) reporting. A grading (severity) scale is provided for each AE term.

SOC
System Organ Class (SOC), the highest level of the MedDRA[1] hierarchy, is identified by anatomical or physiological system, etiology, or purpose (e.g., SOC Investigations for laboratory test results). CTCAE terms are grouped by MedDRA Primary SOCs. Within each SOC, AEs are listed and accompanied by descriptions of severity (Grade).

CTCAE Terms
An Adverse Event (AE) is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may not be considered related to the medical treatment or procedure. An AE is a term that is a unique representation of a specific event used for medical documentation and scientific analyses. Each CTCAE v4.0 term is a MedDRA LLT (Lowest Level Term).

Grades
Grade refers to the severity of the AE. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline:

- **Grade 1** Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- **Grade 2** Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.
- **Grade 3** Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL**.
- **Grade 4** Life-threatening consequences; urgent intervention indicated.
- **Grade 5** Death related to AE.

A Semi-colon indicates 'or' within the description of the grade.

A single dash (-) indicates a Grade is not available. Not all Grades are appropriate for all AEs. Therefore, some AEs are listed with fewer than five options for Grade selection.

Grade 5
Grade 5 (Death) is not appropriate for some AEs and therefore is not an option.

Definitions
A brief Definition is provided to clarify the meaning of each AE term. A single dash (-) indicates a Definition is not available.

Navigational Notes
A Navigational Note is used to assist the reporter in choosing a correct AE. It may list other AEs that should be considered in addition to or in place of the AE in question. A single dash (-) indicates a Navigational Note has not been defined for the AE term.

Activities of Daily Living (ADL)
*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
**Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

[1] CTCAE v5.0 incorporates certain elements of the MedDRA terminology. For further details on MedDRA refer to the MedDRA MSSO Web site (https://www.meddra.org/).

Infections and infestations					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Endophthalmitis	-	Local intervention indicated	Systemic intervention; hospitalization indicated	Best corrected visual acuity of 20/200 or worse in the affected eye	-
Definition: A disorder characterized by an infectious process involving the internal structures of the eye. **Navigational Note:** -					
Enterocolitis infectious	-	Passage of >3 unformed stools per 24 hrs or duration of illness >48 hrs; moderate abdominal pain; oral intervention indicated (e.g., antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated; profuse watery diarrhea with signs of hypovolemia; bloody diarrhea; fever; severe abdominal pain; hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the small and large intestines. **Navigational Note:** Includes Clostridium difficile (c. diff, c. difficile).					
Epstein-Barr virus infection reactivation	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; medical intervention indicated	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; IV intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by the reactivation of Epstein-Barr virus (EBV). **Navigational Note:** Synonym: EBV					
Esophageal infection	-	Local intervention indicated (e.g., oral antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the esophagus. **Navigational Note:** -					
Eye infection	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated; enucleation	Death
Definition: A disorder characterized by an infectious process involving the eye. **Navigational Note:** -					

EXAMPLE OF A TOXICITY TABLE FROM A PH3 TRIAL

	Preselected for R-CHOP		Preselected for R-CVP	
Characteristic	**BR (n = 103), n (%)**	**R-CHOP (n = 98), n (%)**	**BR (n = 118), n (%)**	**R-CVP (n = 116), n (%)**
Nonhematologic AE (grade ≥3) occurring in ≥3% of patients				
Nausea	3 (3)	0	1 (<1)	0
Vomiting	5 (5)	0	2 (2)	0
Abdominal pain	2 (2)	3 (3)	0	3 (3)
Drug hypersensitivity	3 (3)	0	2 (2)	0
Fatigue	4 (4)	2 (2)	4 (3)	1 (<1)
Pneumonia	2 (2)	0	5 (4)	1 (<1)
Infusion-related reaction	6 (6)	4 (4)	7 (6)	4 (3)
Infection	12 (12)	5 (5)	8 (7)	8 (7)
Hyperglycemia	0	2 (2)	1 (<1)	5 (4)
Back pain	0	1 (1)	0	4 (3)
Syncope	1 (<1)	0	0	3 (3)
Dyspnea	2 (2)	2 (2)	3 (3)	1 (<1)
Hematologic laboratory data (grade 3/4)				
White blood cell count	33 (32)	71 (72)[§]	51 (43)	44 (38)
Absolute neutrophil count	40 (39)	85 (87)[§]	58 (49)	65 (56)
Lymphocyte count	63 (61)	32 (33)[§]	74 (63)	32 (28)[§]
Hemoglobin	0	3 (3)	6 (5)	6 (5)
Platelet count	10 (10)	12 (12)	6 (5)	2 (2)

Q&A #2

Is it possible for Canadians to participate in a clinical trial at a US location with the co-operation and co-ordination of their Ottawa hematologist?

With this in mind, is there travel money available for the necessary repeated follow up visits in the US?

WHERE DO I FIND A CLINICAL TRIAL FOR ME?

All clinical trials in North America have to be registered

The registration site for almost every trial is ClinicalTrials.gov

This site is searchable and accessible by anyone with a computer

ClinicalTrials.gov

MYTH #4: I'D GET BETTER TREATMENT AT PMH OR MD ANDERSON

REALITY:

- We have 6 lymphoma doctors, all keenly interested in clinical trials. And 2 new ones coming!
- We have a national expert in Cutaneous Lymphoma, as well as members of national advisory committees and the CCTG in lymphoma and CLL. We co-author national treatment guidelines.
- We have active trials in B cell lymphoma (Myself and Dr. Aw), Hodgkins (Dr. Bence Bruckler), Cutaneous and T cell lymphoma (Dr. Imrie), and CLL (myself and Dr. Aw)
- We strive to have an active trial in all situations, but it is simply not possible to always fill every slot, so we try to be strategic to have trials open that will benefit as many patients as possible.
- One of my roles is as director of the Malignant Hematology Clinical Research Operations Committee
  - It is my mandate to do everything I can to optimize participation in clinical trials, in lymphoma and beyond

		First Line	Second Line	Third Line +
25%	DLBCL	ZUMA-23	LY17	CLIC-01
25%	FL	future trial of Bispecific plus chemo	future trial of tamezetostat plus chemo	CLIC-01
5%	MCL	(OZM-109)	(GloBryte)	MK1026-003
10%	HL	RADAR - HD12	HD11	
5%	WM	BRAWM		MK1026-003 CLIC-01
5%	MZL			MK1026-003 CLIC-01
10%	TCL	(SPI-BEL-301)		
1%	pCNSL	IND244		
15%	CLL	EVOLVE BELLWAVE-011		

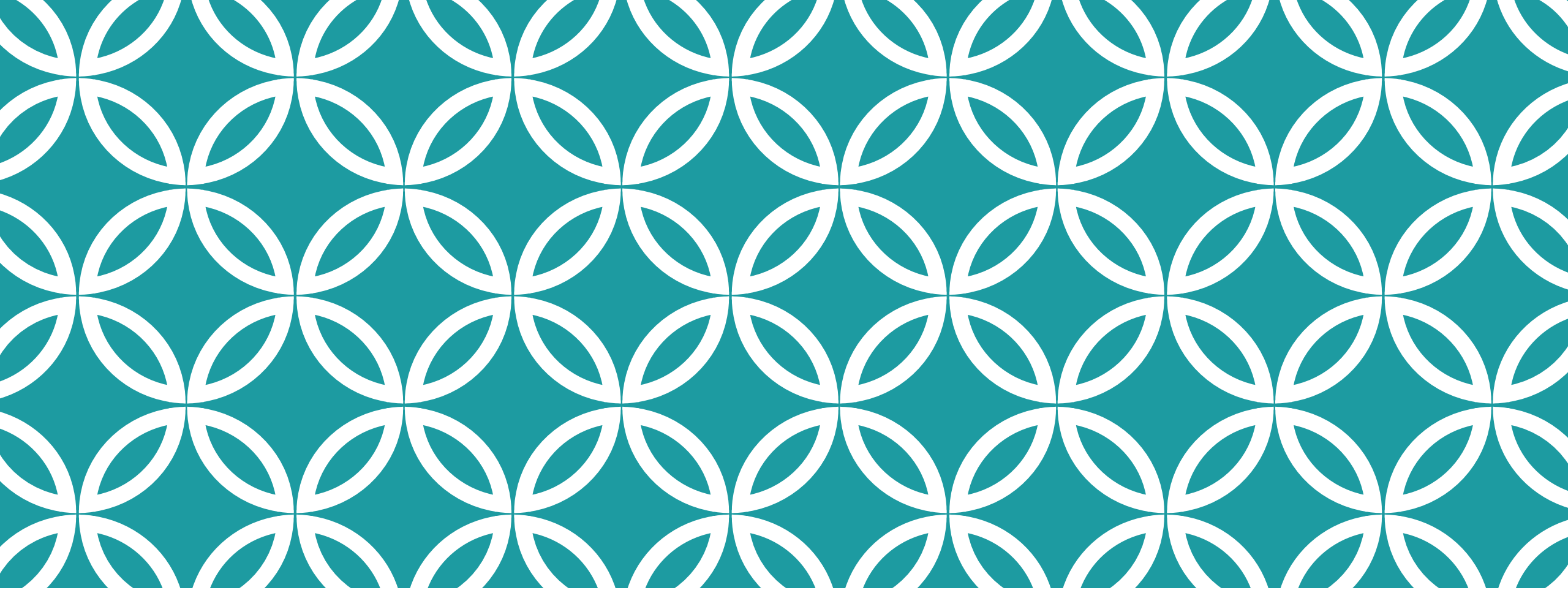
MYTH #5 – CLINICAL TRIALS ONLY BENEFIT THE NEXT GENERATION OF PATIENTS

REALITY – The Unspoken Benefits of Clinical Trials

- Hundreds of patients in *my own career* have participated in clinical trials, and have accessed treatments that proved to improve outcomes in lymphoma. Examples:
  - Rituximab in B-NHL.
  - Brentuximab vedotin in HL.
  - CAR-T in NHL.
  - Acalabrutinib with BR in WM.
  - Bendamustine in iNHL
  - Ibrutinib in WM.
  - Brentuximab vedotin in DLBCL.
  - Romidepsin with GDP in T cell lymphoma
- The 'standard arm' of a clinical trial often contains treatments that are not yet funded in Ontario – they are provided for free on the clinical trial
  - Example – SGN35 study – Brentuximab plus Revlimid and Rituximab versus Placebo plus Revlimid and Rituximab for refractory DLBCL, 2 or more prior therapies – the R and R was provided in both the expt and std arms
- Many patients benefit from participation in **dose reduction clinical trials**
  - Example: the FLYER study in limited stage DLBCL
- Many patients find the increased rigor of clinical trial followup to be a benefit, even if randomized to standard treatment
- Sometimes a clinical trial makes a treatment available where you may otherwise be "out of options"

SUMMARY

- Clinical Trials are conducted under high ethical standards and **should always be considered a treatment option** when available
- It is only through clinical trials that we can move the needle forward on lymphoma and CLL outcomes
- There are many clinical trials available for treatment right here in Ottawa, and if not, your Ottawa lymphoma specialist would help you to find an accessible clinical trial in Canada or elsewhere if it is a good option for you
- Patients who participate in clinical trials do so with some risk, but have the potential to derive several benefits from participation



QUESTIONS AND DISCUSSION