NAVIGATING THE CLINICAL TRIALS EXPERIENCE

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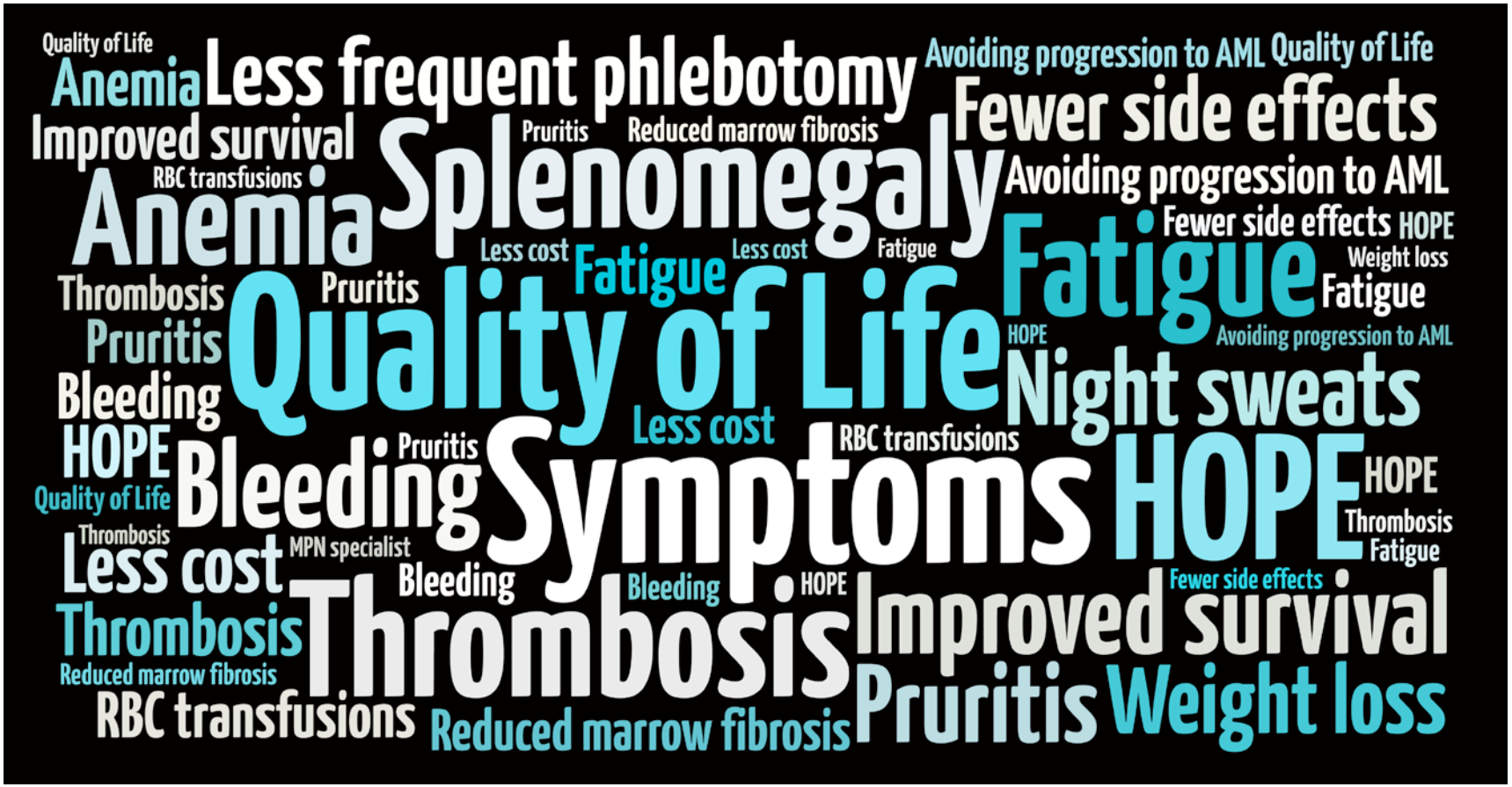
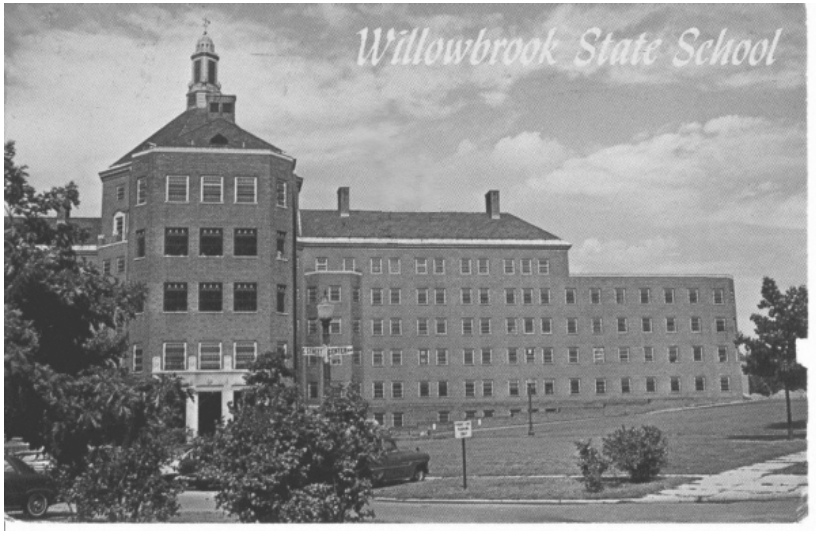
Mayo MPN Patient Conference
February 22, 2015

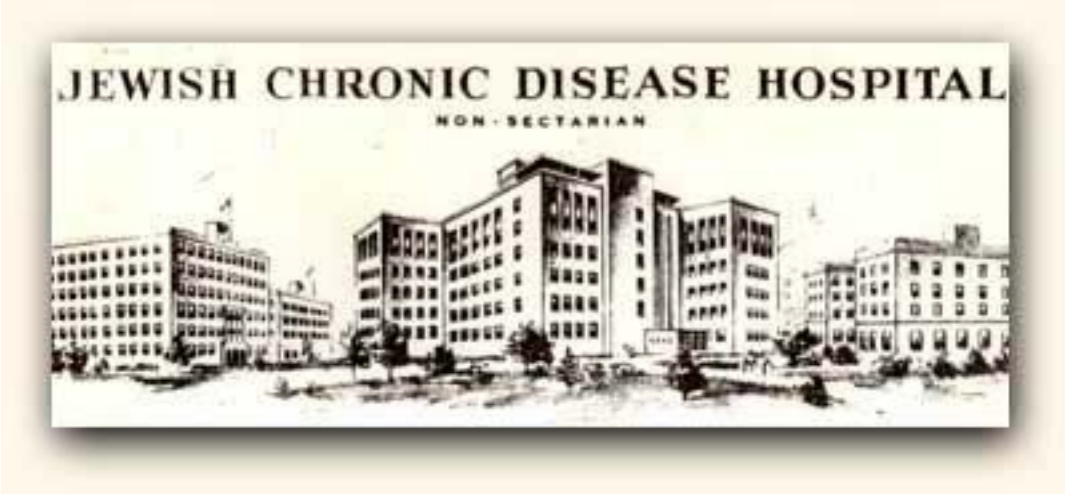
What we talk about when we talk about MPNs



Created by Jason Gotlib

Unethical Clinical Trials: The Burden of History





Oversight of Clinical Trials

FDA

- IND and NDA Review
- Federal audits

Nuremberg Code (1947)
Declaration of Helsinki (1964)
Belmont Report (1978)

Local Institution

- Institutional Review Board & Scientific Review Committee
- Internal Audits / Data Safety Monitoring Committee (DSMC)
- Financial disclosure

Industry

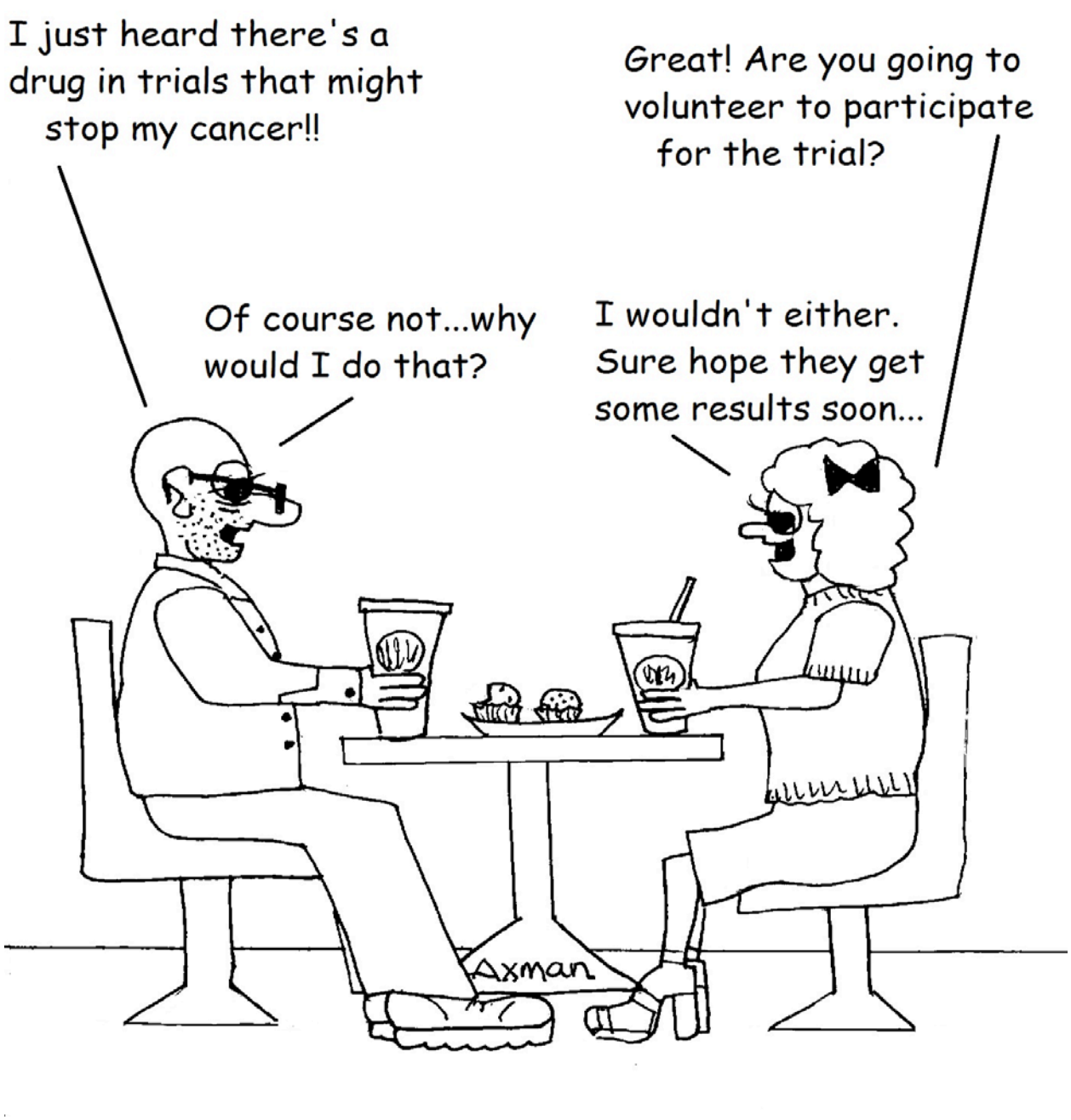
- DSMC
- Monitors
- Distribution of adverse event reports; amendment of consents

Trial Design

- Early stopping rules for safety concerns and lack of efficacy

Barriers to Clinical Trial Enrollment

- Lack of information about available clinical trials
- I don’t want to be a ‘guinea pig’
- Time, travel, or financial constraints
- Concern about receiving low/ineffective dose
- Randomization design; use of placebo; lack of crossover
- Trial eligibility criteria
- Chronologic or biologic age; ageism
- Nihilism on behalf of patients and referring doctors


I just heard there's a drug in trials that might stop my cancer!!
Great! Are you going to volunteer to participate for the trial?
Of course not...why would I do that?
I wouldn't either. Sure hope they get some results soon...
Axman


Personal
Benefit
Altruism

Financial Considerations

- Is the study drug free?
- Are visits, labs, and procedures paid by the trial or by my insurance?
- Are travel and/or lodging expenses defrayed by the study?

Terminology of Drug Status

(FDA)-Approved

- Ruxolitinib in intermediate or high-risk MF
- Ruxolitinib in PV patients with inadequate response or intolerance to hydroxyurea

Off-Label

- PEG-interferon-α in MPNs

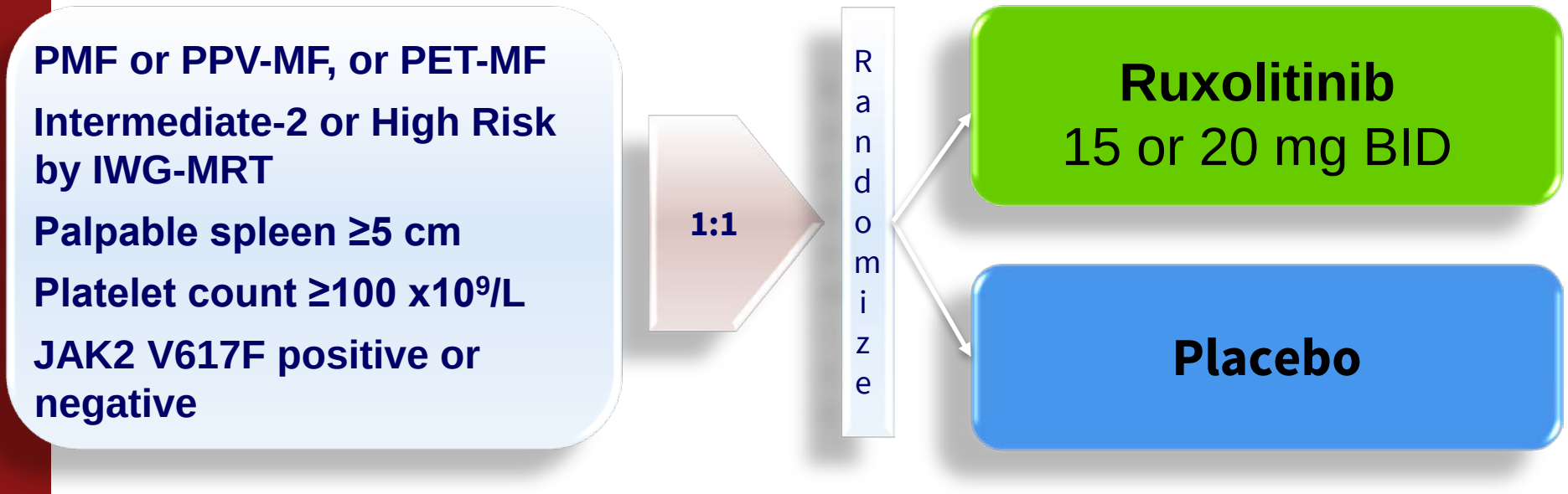
Investigational

- Imetelstat in MF

A Brief Glossary for Patients

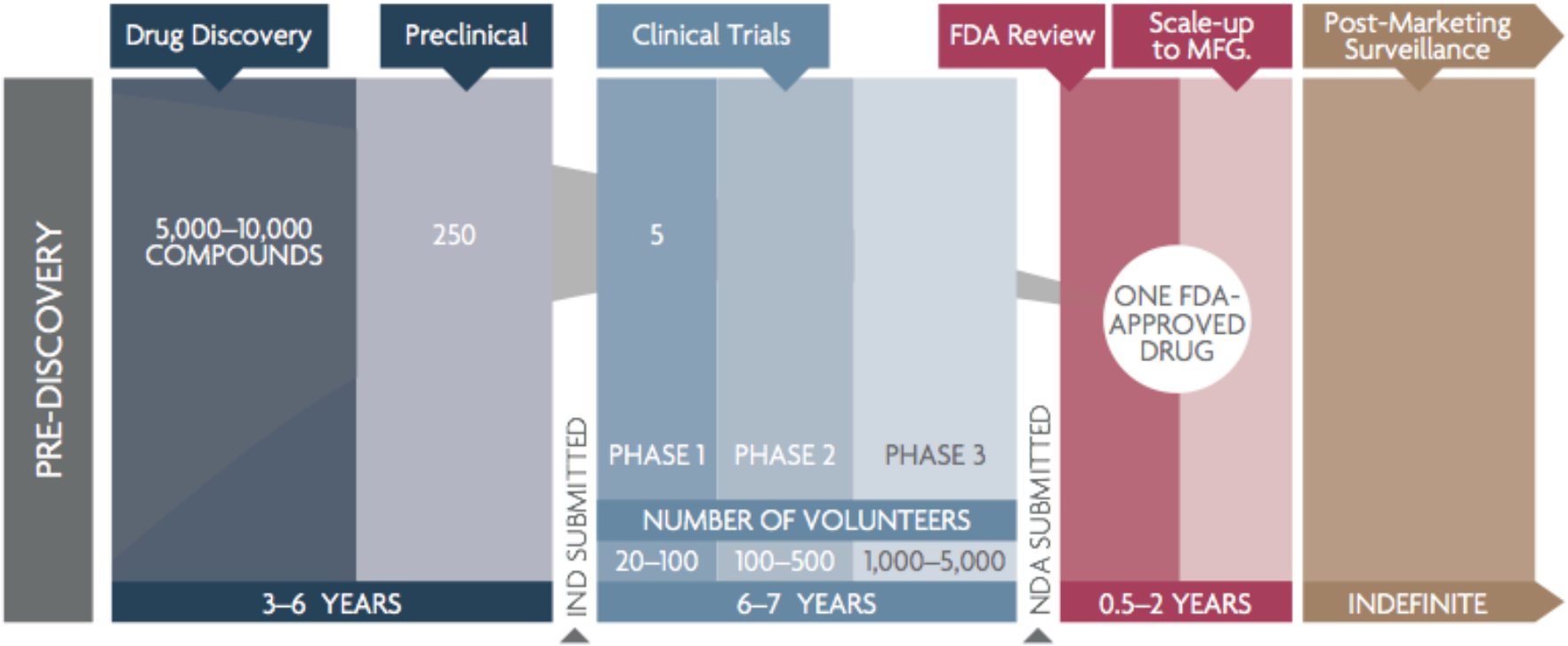
- Open-Label
- Single- or Double-Blind
- Placebo-controlled
- Cross-over design

COMFORT-I: Examples of Clinical Trial Terms



- Study was **double-blind** and **placebo-controlled**
- **Cross-over** to ruxolitinib was possible after week 24
- After cross-over, patients given **open-label** ruxolitinib

Drug Development Timeline



Source: PhRMA[6]

Drug Development Cost: $500 million to 2 Billion

Phases of Clinical Trials

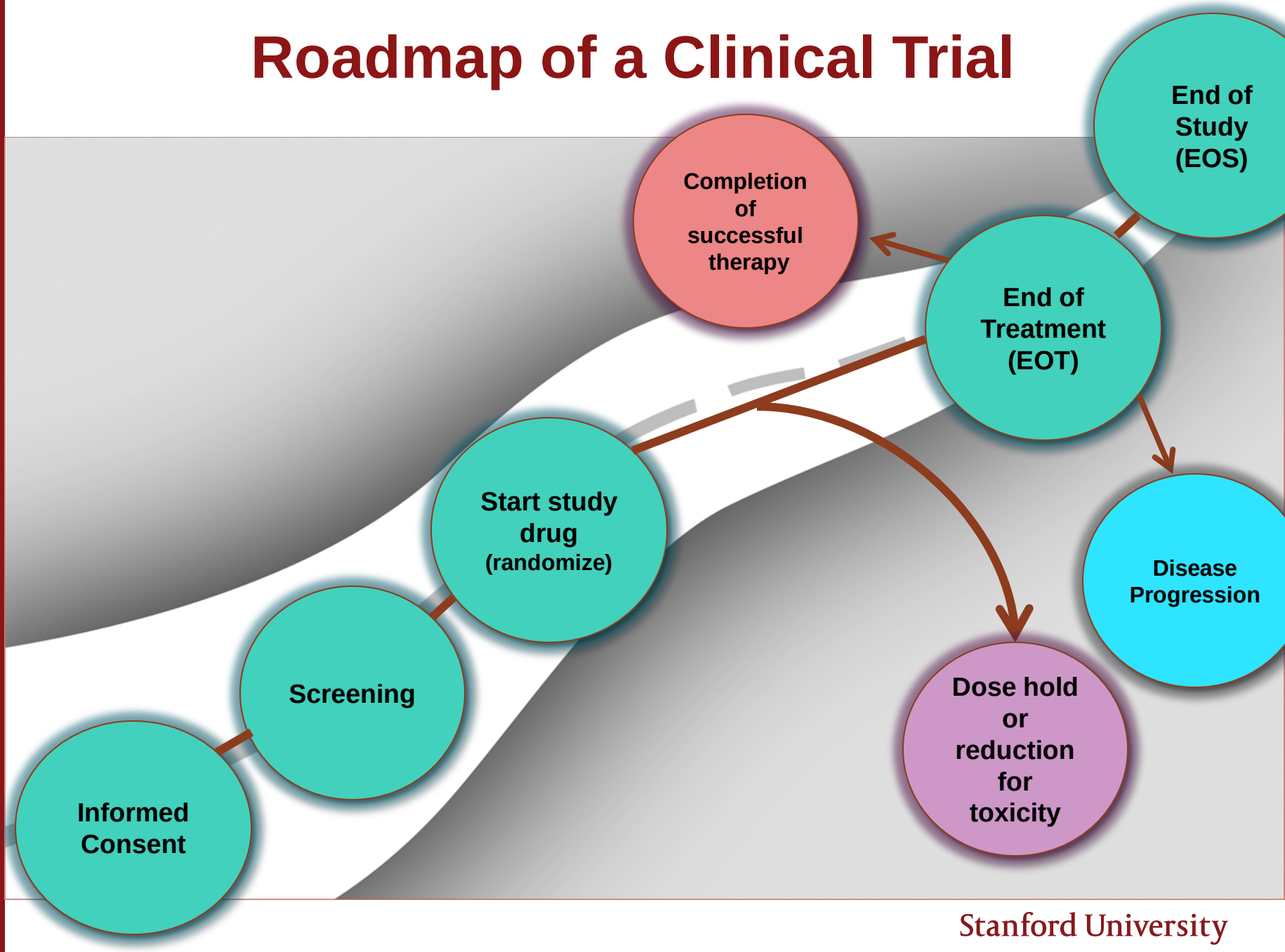
Phase I trials are conducted in healthy volunteers or patients to determine safety and tolerability. Drug doses start low and are escalated in additional cohorts of patients until dose-limiting toxicities (DLTs) are observed. A recommended phase II dose is determined (RP2D).

Phase II trials are used to get an initial reading of efficacy and to further explore safety in small numbers of patients.

Phase III trials are large, pivotal trials to determine safety and efficacy in large numbers of patients in order to obtain drug approval. These are often randomized trials of the drug vs. placebo, best available therapy, or a prior standard of care.

(Phase 4): These are post-approval trials that are sometimes a condition attached by the FDA, also called post-market surveillance studies

Roadmap of a Clinical Trial



Informed Consent (1)

Disclosure requires the researcher to supply the subject with the information necessary to make an autonomous decision

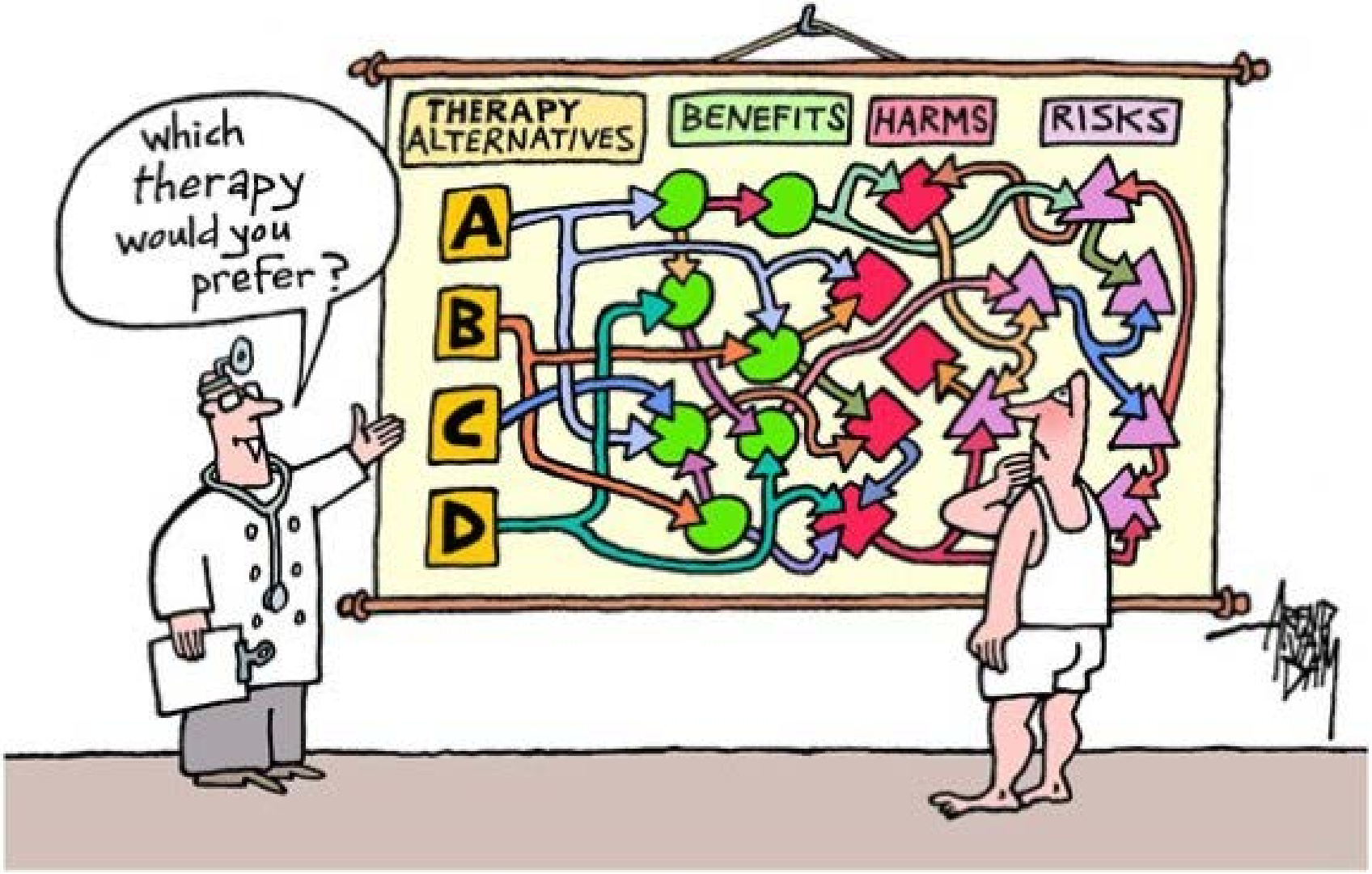
Patients must **have adequate comprehension** of the information provided. This requires that the consent form be written in language suited for the comprehension skills of the subject population. The individual's level of understanding should be assessed during the meeting.

Capacity pertains to the ability of the subject to both understand the information provided, and to form a reasonable judgment based on the potential consequences of his/her decision.

Voluntariness refers to the subject's right to freely exercise his/her decision making without being subjected to external pressure such as coercion, manipulation, or undue influence.

Informed Consent (2)

- How a clinical trial will be conducted
- Which part(s) are experimental
- The risks and benefits of an investigational drug
- The patient's rights
- The alternative treatments available
- All of the periodic testing and examinations required, and for what period of time they will be required
- What testing or medications are paid for by the trial
- Who is responsible for payment of hospitalization or any care needed during or as a result of the clinical trial
- The fact that participation in the clinical trial is voluntary and may be stopped by either the patient at any time, or the clinical trial investigator if either feels it is necessary
- Who a participant should contact with questions or concerns



informed consent

(Cartoon from the Cagle Post by Arend van Dam)

Screening

- Period between signing an informed consent and start of study drug (and/or randomization to a treatment arm). Usually 28-30 days.
- Eligibility criteria are reviewed by the investigator. These are checklists of disease-specific and patient-specific characteristics that all have to be met in order to be enrolled on a clinical trial
- During screening, laboratory tests (e.g. blood and urine), procedures (e.g. bone marrow biopsy, EKG), and imaging (e.g. CT/MRI abdomen/pelvis) are obtained to characterize the status of disease and to make sure that the patient meets inclusion and exclusion criteria
- The screening period is also used to "washout" prior therapies, e.g. allow sufficient time to pass from exposure to prior therapy

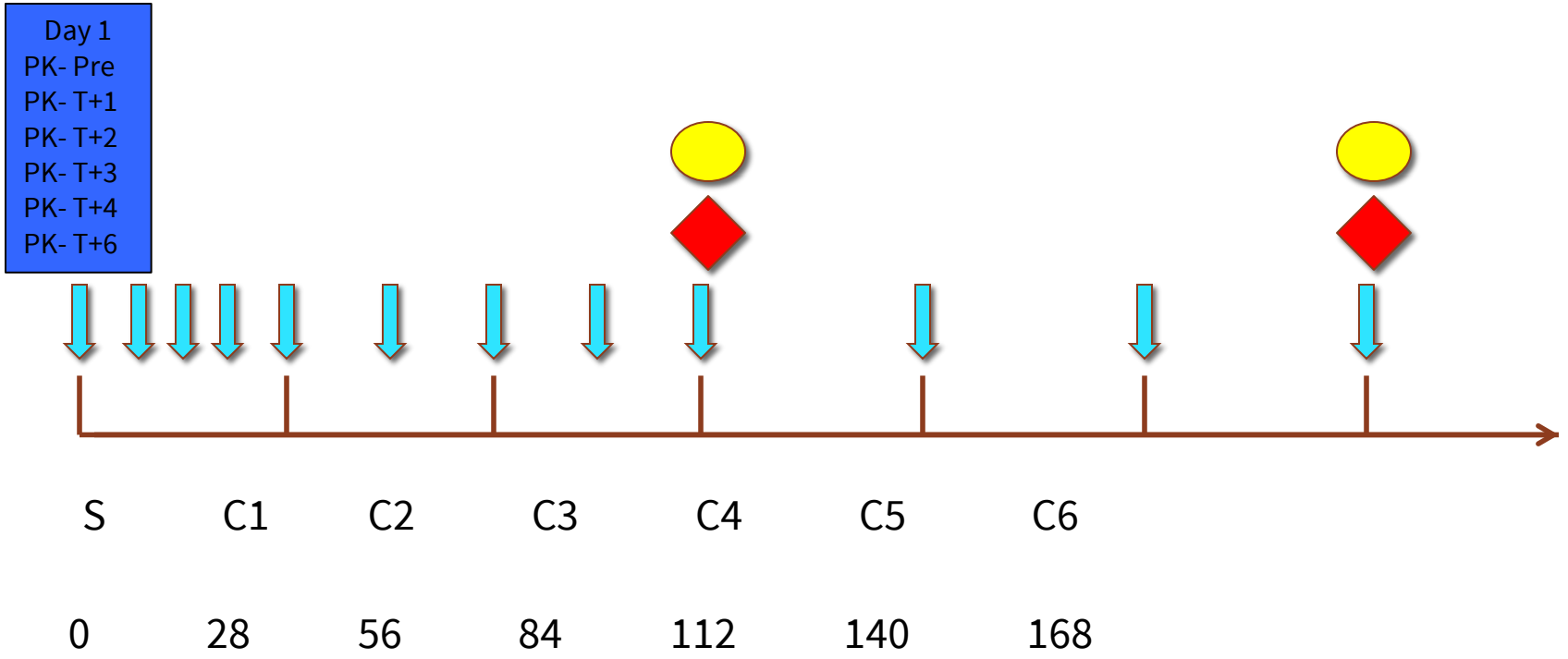
Eligibility Criteria Examples

Intermediate or high risk MF
Splenomegaly > 5cm below left costal margin

Serum creatinine < 2.0 mg/dL
Liver function: AST and ALT < 2.5x ULN
Total bilirubin < 1.5x ULN

No prior JAK inhibitor therapy in the last 14 days; no use of interferon in the last 28 days

Treatment and Schedule of Procedures

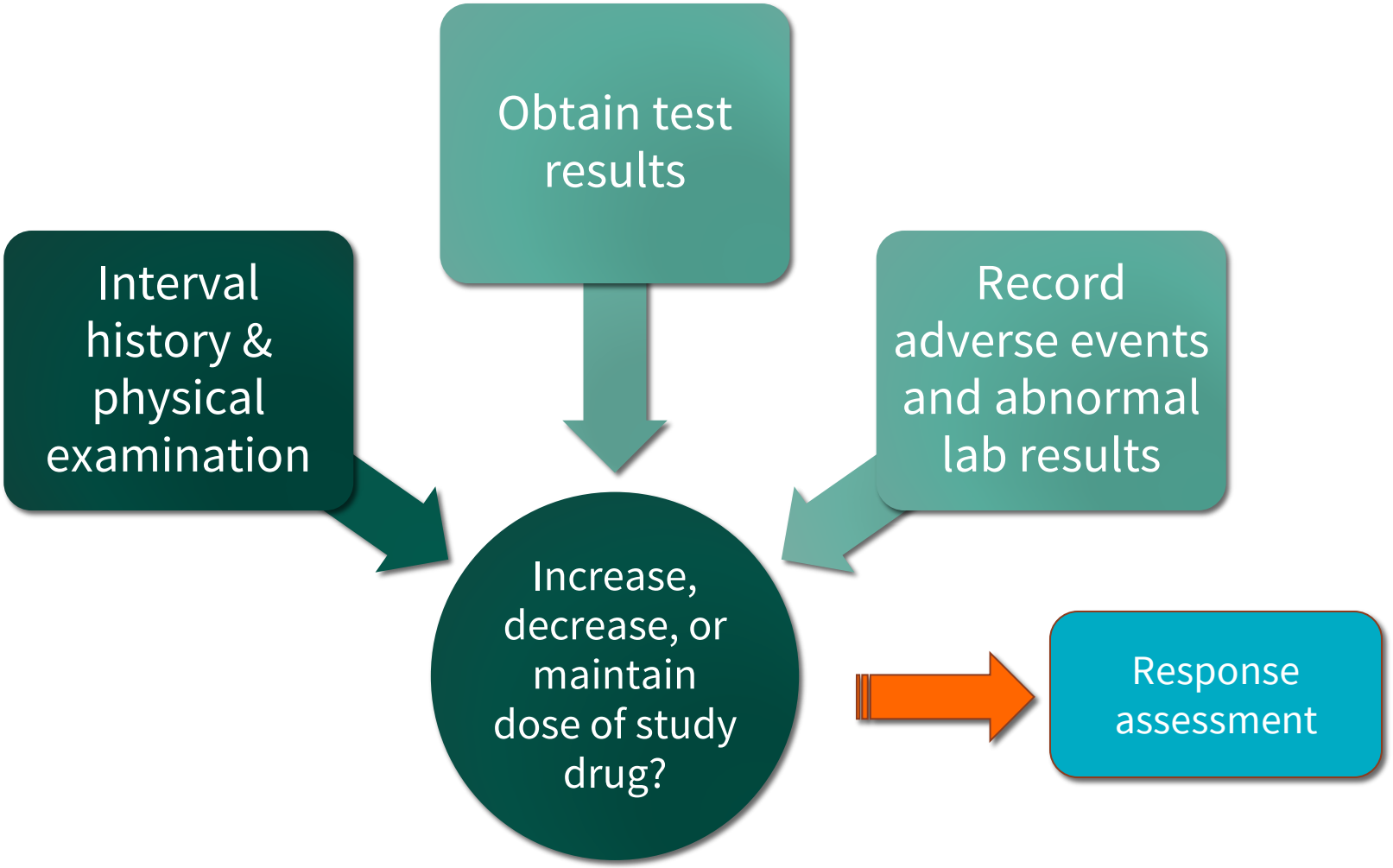


Visit with investigator and blood draws

Bone marrow biopsy

CT or MRI abdomen/pelvis

A Typical Visit on Trial



End of Treatment

- The patient completes the required time on study and is still showing clinical benefit
- The patient demonstrates progressive disease and is too sick to continue, or the protocol requires the patient to stop treatment
- The patient exhibits unacceptable toxicity and is required to stop the study; or the dose cannot be decreased further after prior dose reductions
- Patient or investigator choice
- Death on study (due to disease or study drug or other reasons)
- A follow-up visit in 30 days may be required (EOS); patients may be followed for long-term survival by telephone

The Good Clinical Trial Patient (1)

- Carefully reviews the consent form and asks questions
- Details prior and current medications and allergies
- Compliant with study medication
- Adheres to the trial schedule
- Immediately informs the trial team of new, concerning symptoms
- Contacts the study team before taking new medications or if admitted to the hospital

The Good Clinical Trial Patient (2)

- Partners with family and friends to increase support
- Patient as diarist
- Self-advocacy

Clinical Trials: The Gateway to Trying to Improve Efficacy while Minimizing Toxicity

Drug with new mechanism of action

Ruxolitinib, a JAK inhibitor, in MF

PRM-151, an anti-fibrotic, in MF

Imetelstat, a telomerase Inhibitor, In MF

Different drug with same mechanism of action

Fedratinib, **Momelotinib**, **& Pacritinib**, alternative JAK inhibitors, in MF

Combination therapy

Ruxolitinib +

LDE225

or

BKM120

or

Panobinostat

Same drug, new indication

Ruxolitinib in PV patients with inadequate response to, or intolerance to hydroxyurea

Resources for MPN Education & Finding a Clinical Trial

- **Your local hematologist**
- **MPN specialist at an academic medical center**
- **Patient support groups**
- **Online / social media**

Search engine of registered clinical trials:
www.clinicaltrials.gov

MPN Education Foundation:
www.mpninfo.org

MPN Research Foundation:
www.mpnresearchfoundation.org

MPN Advocacy & Education International:
www.mpnadvocacy.com

MPN ADVOCACY & EDUCATION INTERNATIONAL

MPN RESEARCH FOUNDATION
advancing blood cancer research

Acknowledgements

Stanford

Jim Zehnder
Jason Merker
Andy Fire
Andrea Linder
Cristina Daniels
Cheryl Langford
Cecelia Perkins
Jenny Ma
Lenn Fechter

Mayo Clinic, Scottsdale

Ruben Mesa
John Camoriano

Our Patients & Their Caregivers

Community of MPN Investigators

Funding:
Charles and Ann Johnson Foundation