The Life Raft GROUP

Real World Evidence (RWE) in Rare Cancers Such as GIST

The Life Raft Group (LRG)

- Dying leiomyosarcoma patients
- Lack of effective treatment

Discovery of the c-Kit Enzyme lead to a diagnosis of GIST (Gastrointestinal Stromal Tumor)

Imatinib (Gleevec) is found to target CML, then GIST

- Patients are walking out of their deathbeds

Through the power of the Internet, a GIST community was created

- Norman Scherzer, Executive Director, develops relationships with key influencers, such as Novartis' Dan Vasella

The Life Raft Group is born

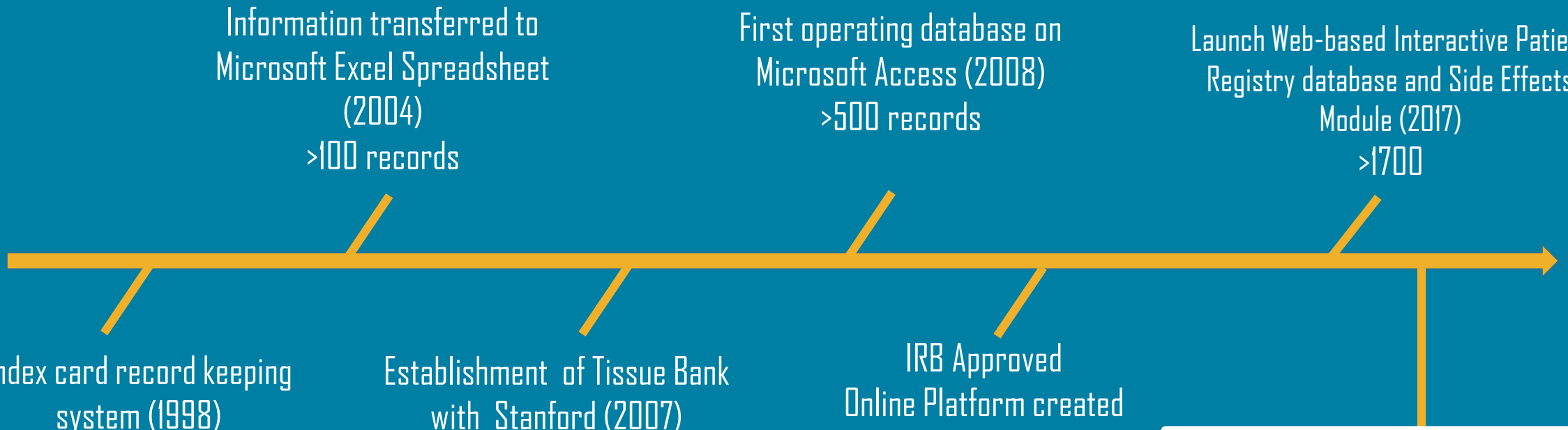
The LRG and Real World Evidence

- GIST was a new functional diagnosis and Gleevec (imatinib) a new type of targeted treatment.

- The patient perspective is at the heart of our real world data.
- We began collecting data from our patients.
- Our Patient Registry was born.

- Combined with our GIST Collaborative Tissue Bank, we began identifying valuable real world evidence that has the potential to save lives and improve quality of life for GIST patients.

LRG Patient Registry Timeline



LRG Patient Registry Today

Total Patients: >1800

Total # of Tissues: 778

Countries: 88

Since the creation of the LRG, cancer diagnosis and treatment has changed dramatically

What is Real World Evidence ?

- Real world evidence utilizes observational data to determine the perceived benefit of treatments to increase survival and improve quality of life for cancer patients.

- “Real world data relates to patient health status and/or the delivery of health care routinely” - FDA

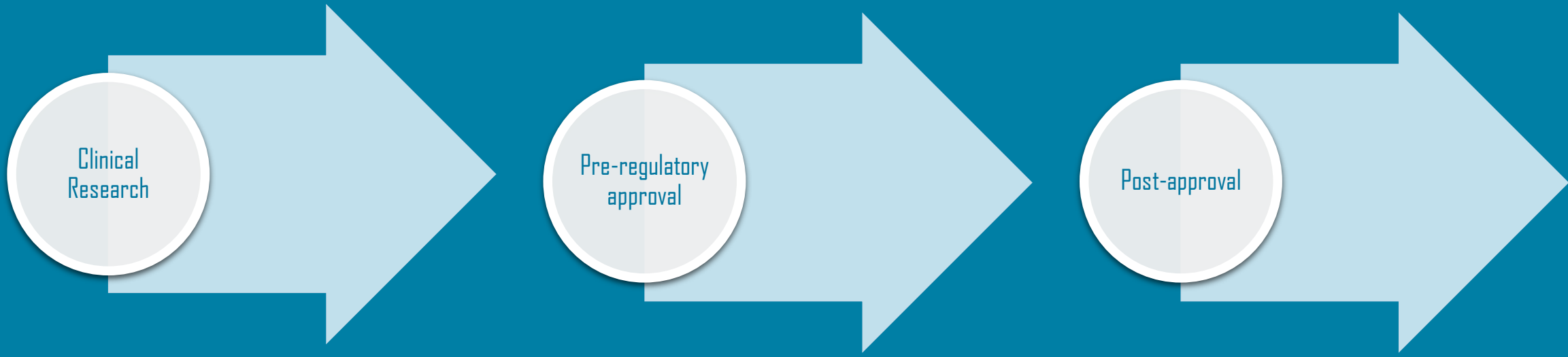
Why is Real World Evidence important?

The rich diversity of data collected from patients will yield to more precise, better targeted, and therefore more highly effective health care.

Where does it come from?

RWE is derived from real world data associated with patient's outcomes as experienced in actual practice.

The role of RWE in drug development



RWE:

Expedites generation of research hypotheses and recruitment of patients.

Provides a better insight on safety and effectiveness of new drugs.

Identifies factors that are difficult to identify after time of approval

Real world data and resultant real world evidence is being utilized to **enhance and complement traditional research**

Clinical Trials and RWE

Clinical Trials	RWE
Can it Work?	Does it Work?
To Gain Regulatory Approval	To Influence Clinical Practice
Ideal Conditions	Real World Conditions
Fixed Regimen	Flexible Regimen
High	Low to High
Low to Medium: Homogeneous Populations	High: Heterogeneous Populations
High	Variable

* John P. New et al, "Obtaining Real-World Evidence: the Salford Lung Study," Thorax (2014): 1-3, accessed May 11, 2015, doi:10.1136/thoraxjnl-2014-205259.

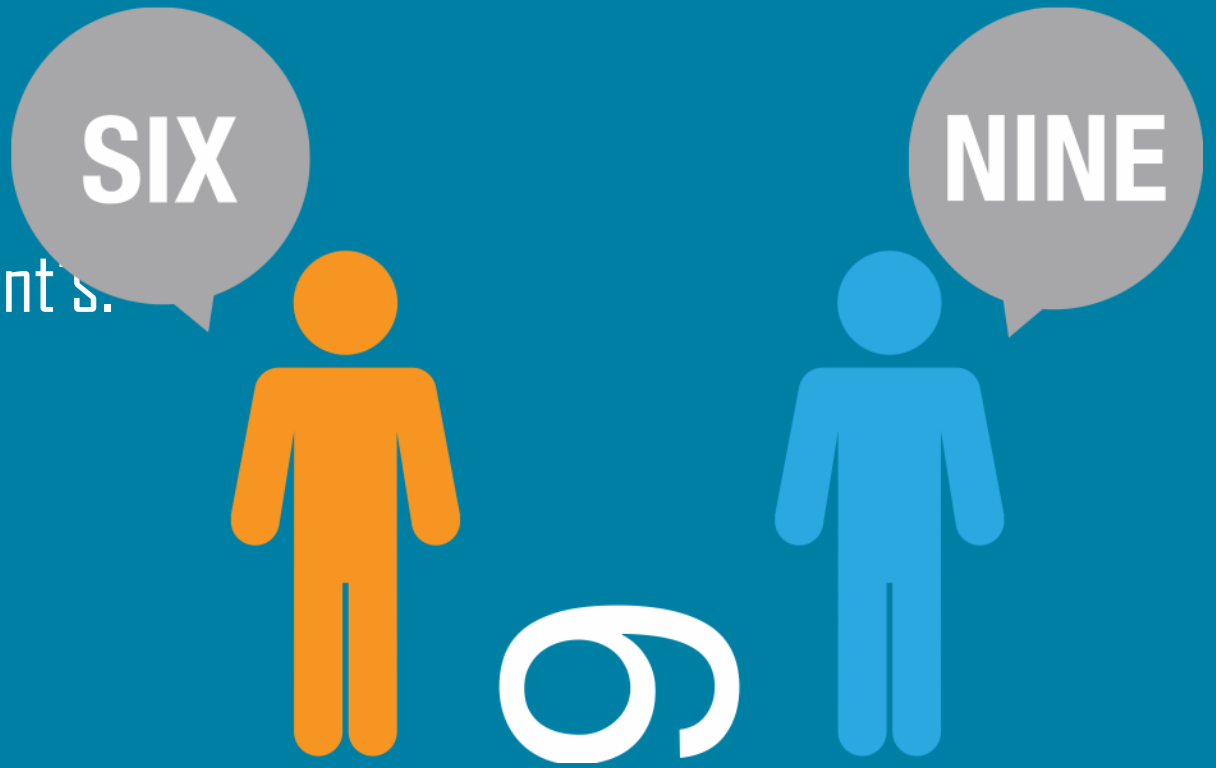
Clinical Trials

Evidence, derived from clinical trials, has conventionally been considered to be the "gold standard". Data collected is closely controlled and monitored. However, patients recruited are not always representative of the general population of GIST patients.

Limitations in Clinical Trials

1. Lack of patient's perspectives

Traditional approaches are based on physician's perspective not the patient's.



Three perspectives

PATIENT	CLINICAL TRIALS	RWE
Presents daily sporadic episodes of diarrhea “ I have to give up my job, due to my frequent daily episodes of diarrhea”	Toxicity Scale (0-4) <5 episodes every 24hrs: **Rate 1**	Quality of Life (1-10) Interfering with normal activities: **Rate 7**

2. There is a time lag between discovery and effectiveness of a drug

Real Side Effects, Real People

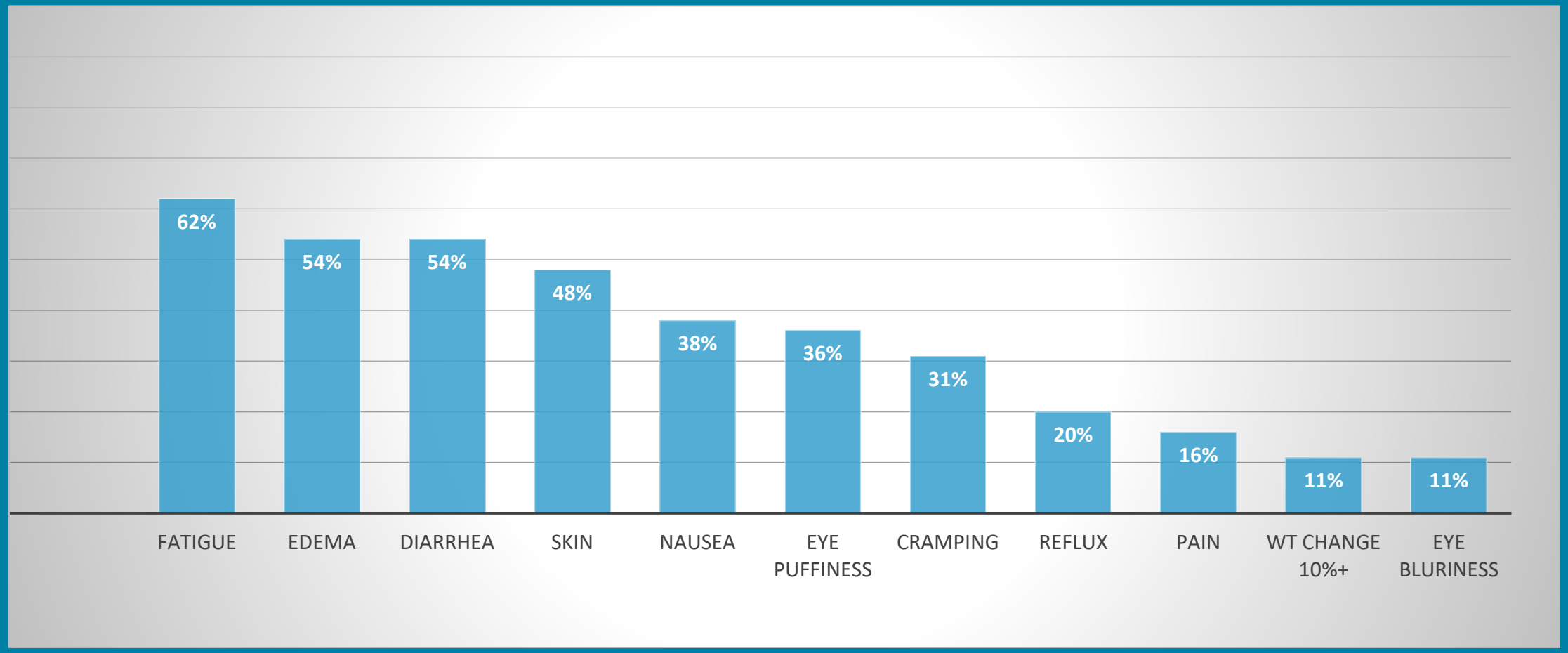
April 2001, The LRG presented its first side effects survey of patients on Gleevec

- Sample size (n): 61
- Fatigue, edema, and diarrhea - most common side effects.
- Side effects in females were more severe.

The Survey

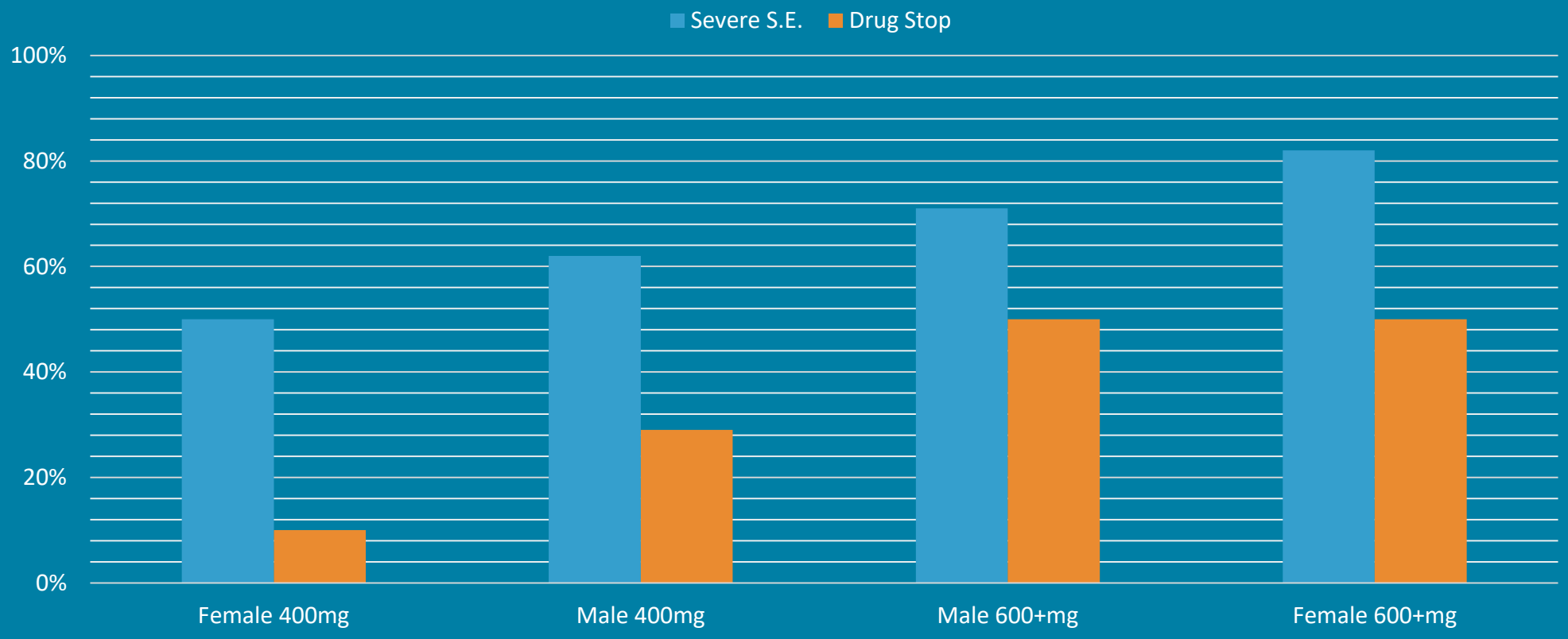
- Respondents were asked to describe and rank each of their side effects
- S.E. was rated SEVERE is the average rating was 7 or higher or if patient cited a reason for stopping or lowering drug
- Lastly, patient was asked to describe the functional effect of the S.E.

Reported Major Side Effects



Gender and Drug Correlation

Females (47%) reported one or more severe side effect when compared to males (18%).



3. Overall survival (OS) is difficult to measure

- OS is harder to achieve due to timing, thus clinical trials use median overall survival (MOS) or time-dependent endpoints
- Depending how a clinical trial is designed, it is able to measure only progression free survival (PFS) among patients
- Overall survival can't be measured if a clinical trial has a placebo with a crossover
- Most clinical trials don't track patients over time

LRG Patients Have Higher Survival Rate

Study	Treatment line	N	OS (months)	% difference in OS	PFS (months)
Phase III Imatinib trial [1]	1	695	52		19
LRG Registry: Imatinib	1	1034	87.0	+67%	31.0
Phase III Sunitinib trial [2]	2	207	17.0		6.3
LRG Registry: Sunitinib	2	436	32.3	+90%	8.4
GRID Phase III Regorafenib trial [3]	3+	199	17.4		4.8 (7.4 - investigator assessment)
Italiano Regorafenib Study [4]	3	223	9.2		3.6
LRG Registry: Regorafenib	3	344	21.5	+24% vs GRID +134% vs Italiano	4.6

[1]. Heinrich et al. 2017; [2]. Demetri et al. 2012; [3]. Demetri et al. 2013; [4]. Italiano et al. 2011

4. Researchers often prioritize competition over collaboration

Results are often held back until publication, making clinicians and patients wait a long time until hearing about potentially life saving findings

What can RWE offer clinicians and patients?

- **Accuracy**: Including rigorous quality controls
- **Timeliness:** Reduces lag between discovery and publication
- **Reflectiveness:** Of patient's perspective about treatment efficacy and side effects
- **Completeness**: From initial patient's diagnosis to end of life across institutional and geographic barriers
- **Portability:** As patient moves to a new trial or treatment site
- **Support:** For clinical trial recruitment and other specialized data

The Life Raft Group RWE in action

Project InterGR™

Patient Registry

GIST Collaborative Tissue Bank

SideEQ

Project Surveillance

Pediatric & SDH-Deficient Consortium

LRG Patient Registry

GIST/PRIME

- The largest GIST registry in the world
- It is an ongoing research study where GIST patients and caregivers volunteer their information regarding their GIST treatment.
- RWD is used to understand the natural history of GIST, treatment outcomes, and help accelerate research
- GIST/Prime was created for patients and caregivers.

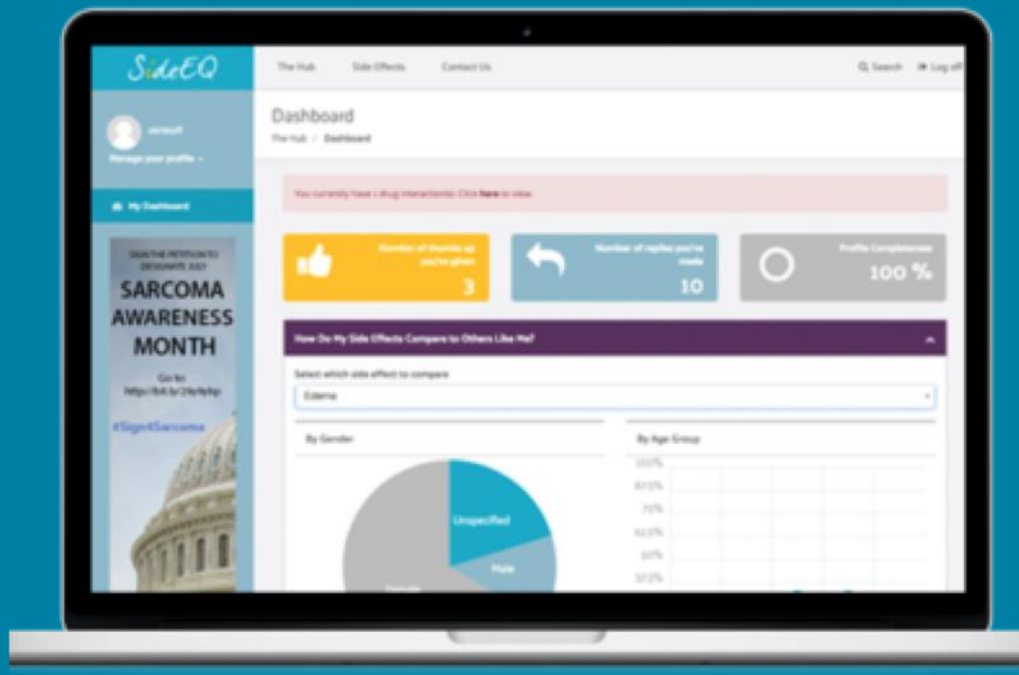
GIST Collaborative Tissue Bank

- For patients, it's an opportunity to accelerate GIST research while tailoring their care to their mutation.

- For researchers, it's an opportunity to access tissue linked to GIST clinical histories and to share valuable tissue and critical data.

SideEQ

SideEQ helps patients manage their side effects and potentially and potentially improve adherence.



At its heart, SideEQ is based on collaboration:

Between the LRG and patients, among patients (both within and across diseases), and between patients and researchers.

They all have one thing in common – the desire to improve the quality of life of patients.

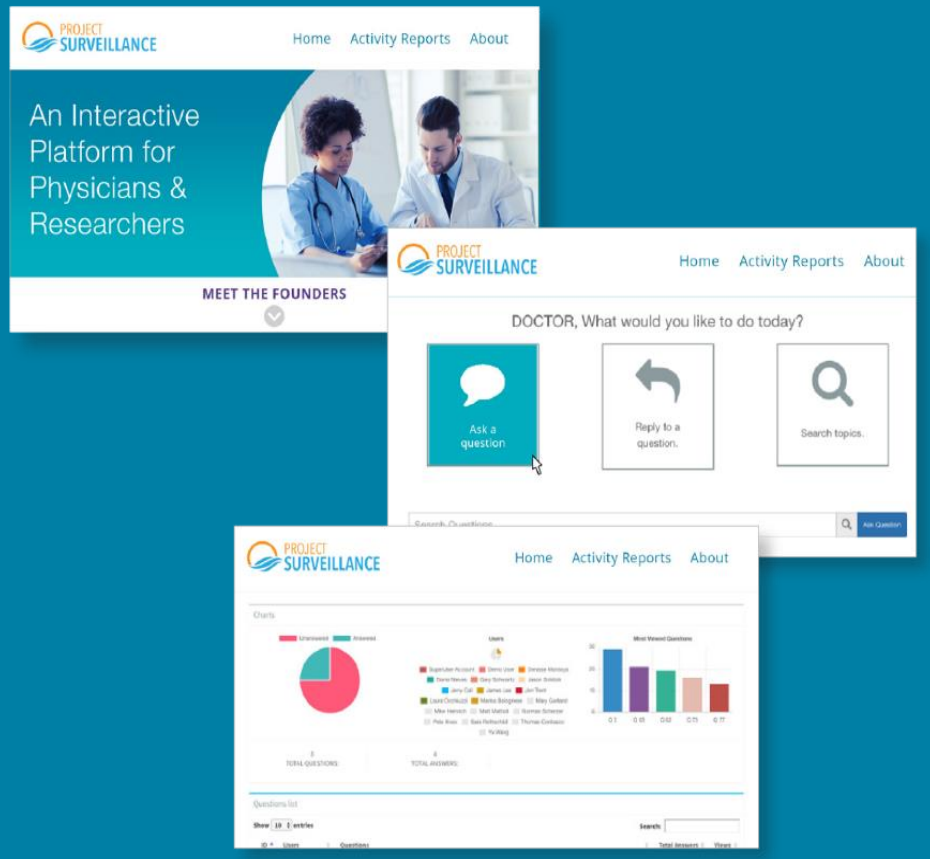
PROJECT SURVEILLANCE

An Interactive Platform for Physicians & Researchers

Project Surveillance:

- Is a platform for GIST specialists to share their data, plus the rich data from the LRG's Patient Registry.
- Aims to form a collaborative platform for GIST experts to share real-world, real-time observations in a timely, actionable manner.

Clinical decision making will become smarter.



LRG Consortiums

- Pediatric & SDH-Deficient Consortium
- Salud con Datos
- Columbia, New York-Presbyterian
- FDA/Pharma/Academic Collaboration

Pediatric & SDH-Deficient Consortium

Collaborative effort of leading Pediatric and SDH-Deficient GIST experts aiming to dramatically impact patient survival and quality of life through data and tissue sharing.

List of members: July 2018

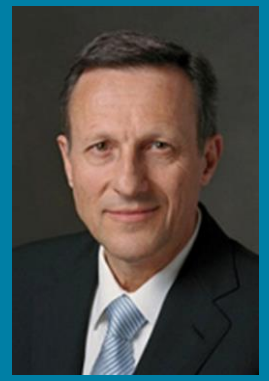
Name	Institution
Fernanda Arnaldez	Pediatric Oncology Branch/National Cancer Institute
Venkata Ramesh Bulusu	Bedford Hospital NHS Trust & Cambridge University Hospitals
Ruth Casey	Bedford Hospital NHS Trust & Cambridge University Hospitals
Suzanne George	Dana Farber Cancer Institute
Eyal Gottlieb	Technion-Israel Institute of Technology
Michael Heinrich	Oregon Health and Science University
Lee Helman	Childrens Hospital of Los Angeles
Katherine Janeway	Dana-Farber Cancer Institute
Jonathan Keith Killian	National Institutes of Health/Cancer Genetics Branch
Michael P. LaQuaglia	Memorial Sloan Kettering Cancer Center
Markku Martti Miettinen	National Cancer Institute
Karel Pacak	National Institutes of Health
Jason Sicklick	Moores Cancer Center, UCSD
Constantine Stratakis	National Institutes of Health
Jonathan Trent	Sylvester Cancer Center

Testimonials

Tom Ferguson, MD of the Ferguson report: “The man many consider the George Washington of e-patient-directed medical research is Norman Scherzer…who says that ‘One of the great benefits of patient-initiated research is its speed’ ”.

Janet Woodcock, Director, Center for Drug Evaluation and Research, US Food and Drug Administration: In respond to the LRG Columbia Collaborative Project “Great work! wish you the best of luck, this is what needs to be done.”

"The new research model pioneered by the Life Raft group is making it possible for patients and family members to contribute to clinical research for their diseases in unprecedented ways," says George Demetri, medical director of the Center for Sarcoma and Bone Oncology at Boston's Dana-Farber Cancer Institute.



Daniel Vasella, MD, Former-CEO of Novartis: “Norman showed me his statistics because he was a scientist. He collected all the data and he knew much more than we knew. You know what, he was right. We were wrong. The dose had to be higher. I believe Anita is alive not because of us but because of you.”

Future RWE collaborative projects

- Global Surveys
- Generics
- Plasma/Mutational Testing
- Side Effects Data
- GIST Specialists
- Regional/Global Patient Registry