

Definition of dose-limiting toxicity in phase I cancer clinical trials of molecularly targeted agents

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Conflicts of interest

- None to disclose

Introduction

- Assessment of **dose-limiting toxicity** (DLT) and establishment of the maximum tolerated dose (MTD) constitute the **primary endpoint** of phase I cancer trials
- **Guidelines** for the use and reporting of **endpoints** in phase II/III randomized trials (CONSORT)
- **No consensus** on the definition of DLT in phase I trials

Introduction

- Necessity for **standardization** of the **definition of DLT** in phase I trials?
- Question raised during the 9th NCI/EORTC New Drug Development Symposium in Amsterdam in 1996
- Recommendation was to try standardizing the definition of DLT
- Time of **cytotoxic agents**

Introduction

- Molecularly targeted agents (MTA) display **different toxicity profiles**
- Efficacy of these agents **may not increase** with dose
- The **recommended phase II dose** is still largely based on the determination of the MTD and therefore on the assessment of DLT

Objective

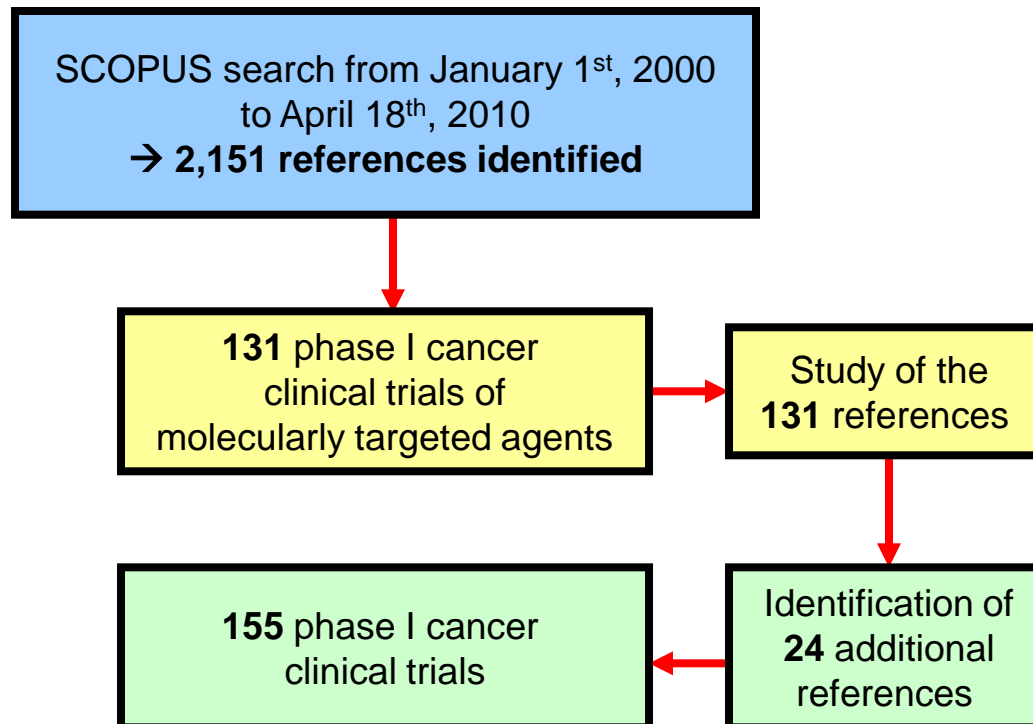
To evaluate how **DLT** are defined in **phase I** cancer clinical trials of **MTA** administered as **single agents** published over the last decade

Methods

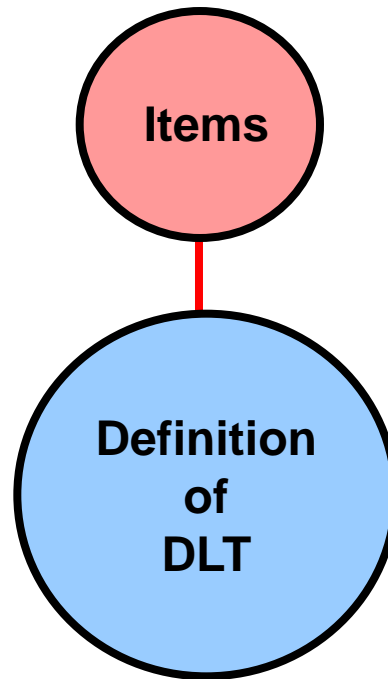
Selection of trials:

- MTA
- immunotherapeutics and hormone therapies were excluded
- **PO** or **IV** administration

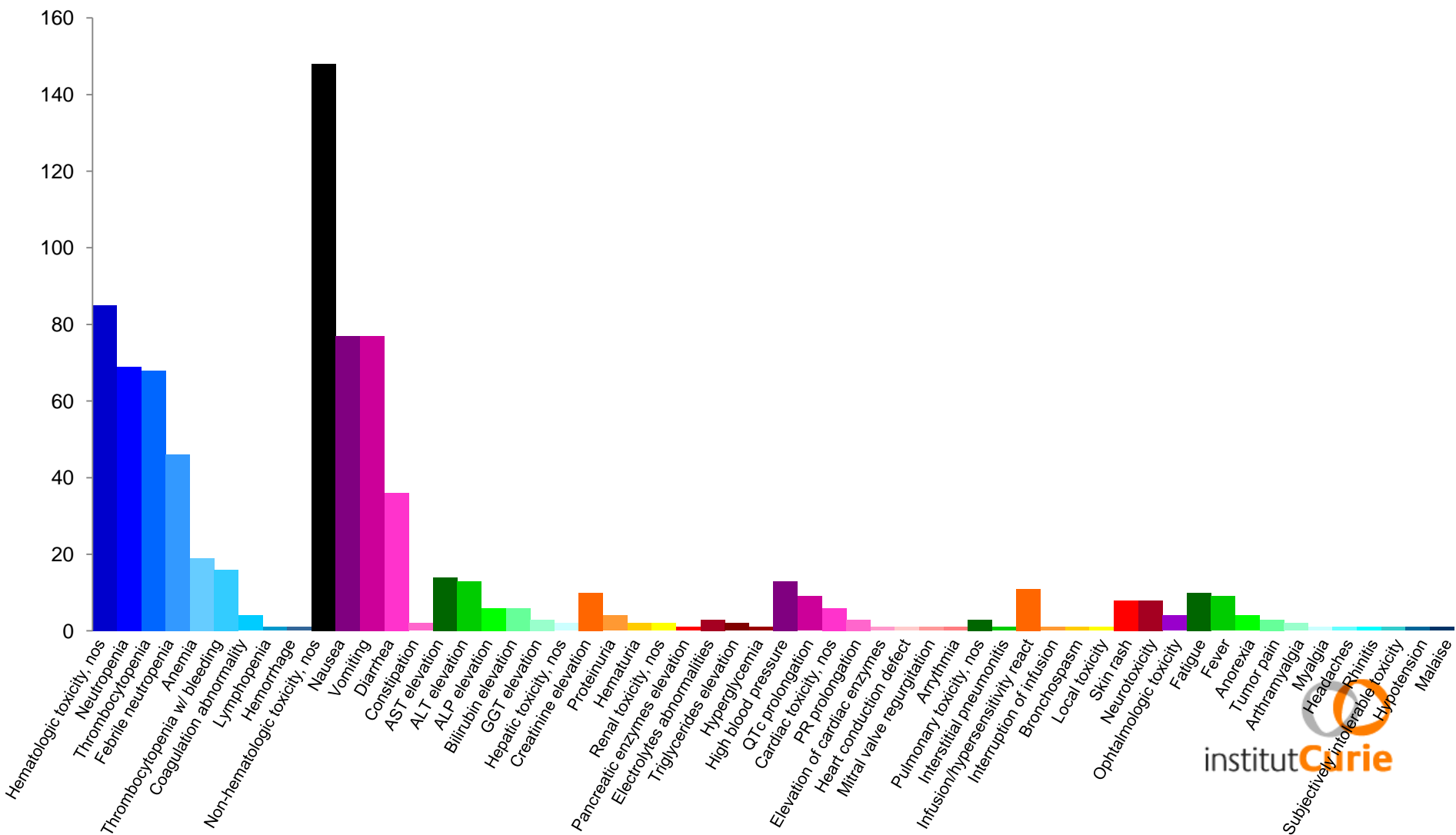
General results



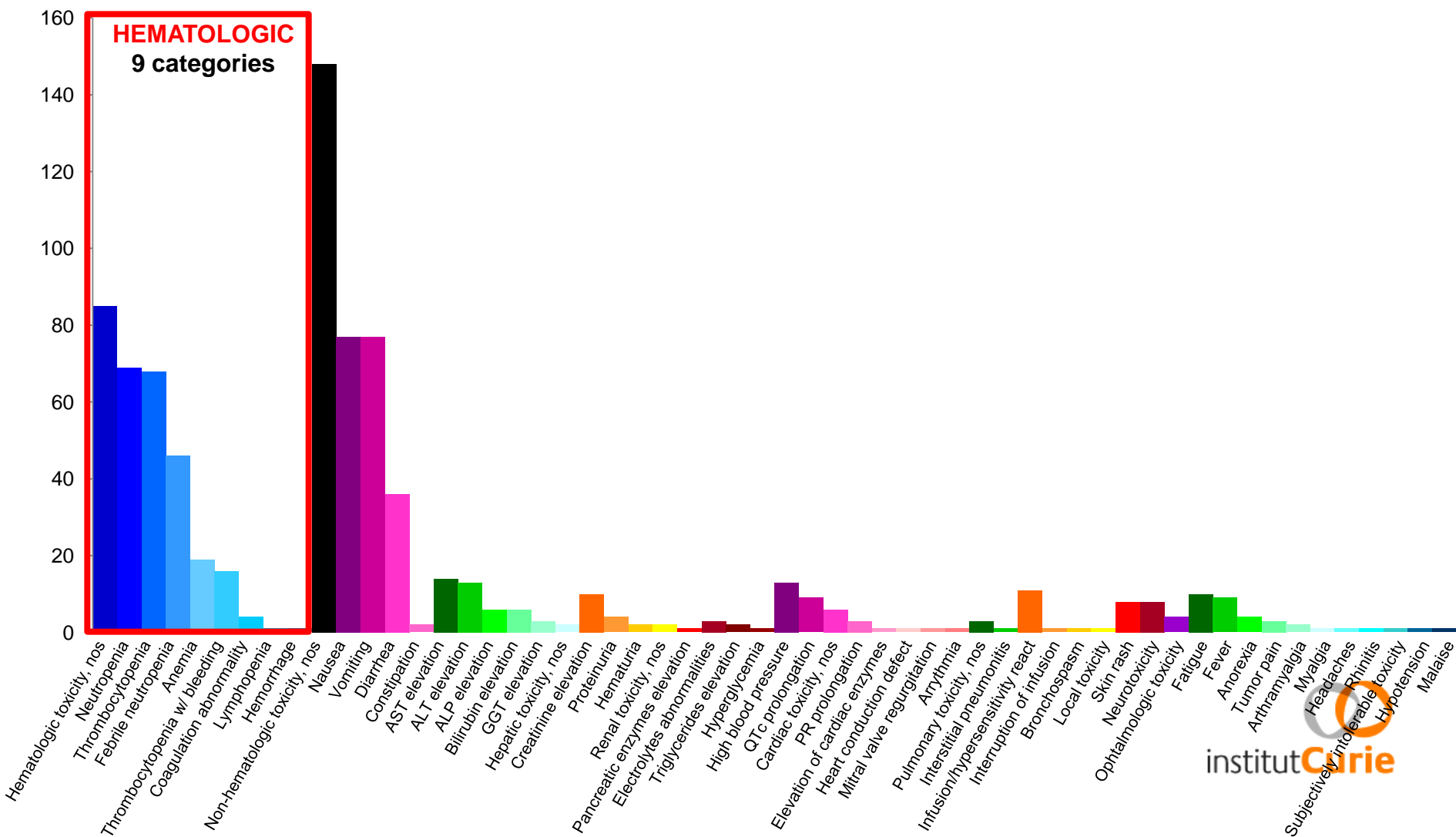
Items used to define DLTs



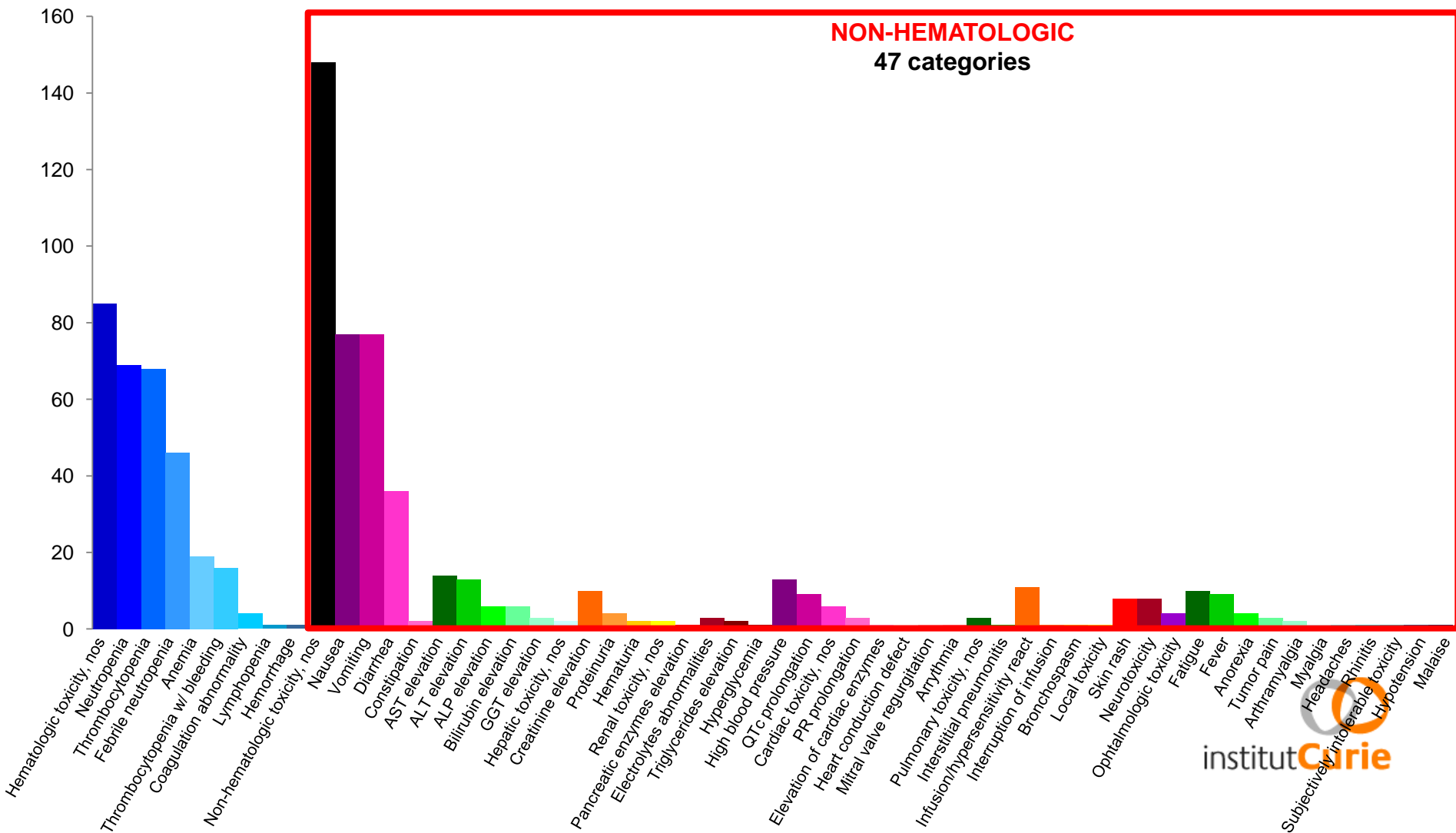
Items used to define DLTs



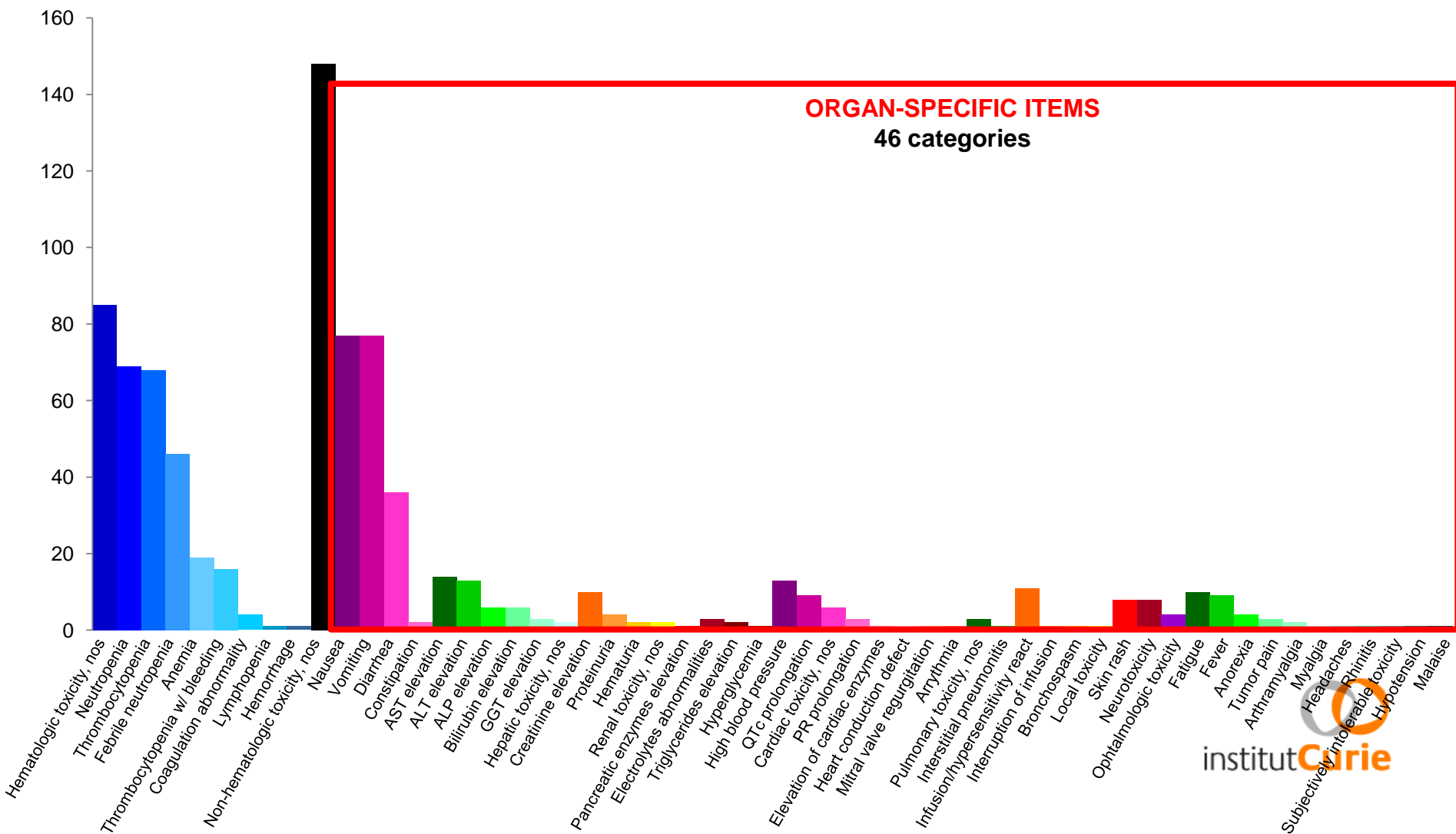
Items used to define DLTs



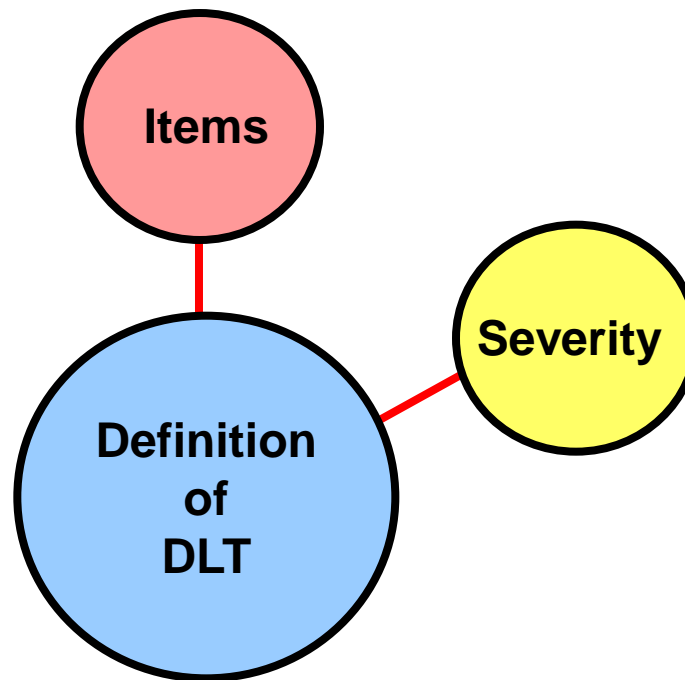
Items used to define DLTs



Items used to define DLTs



Severity of toxicity



Severity of toxicity

 NCI CTCAE \geq G2

 NCI CTCAE \geq G3

 NCI CTCAE \geq G4

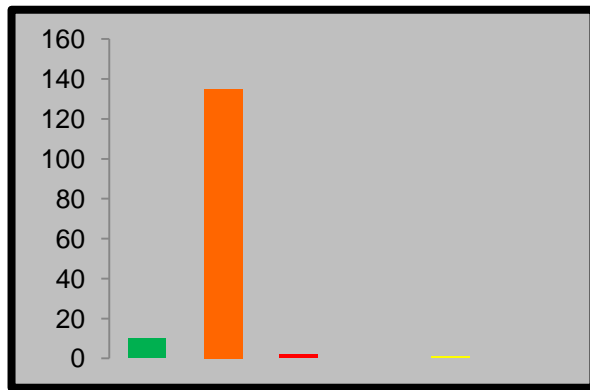
 Not a DLT

 Other classification/threshold

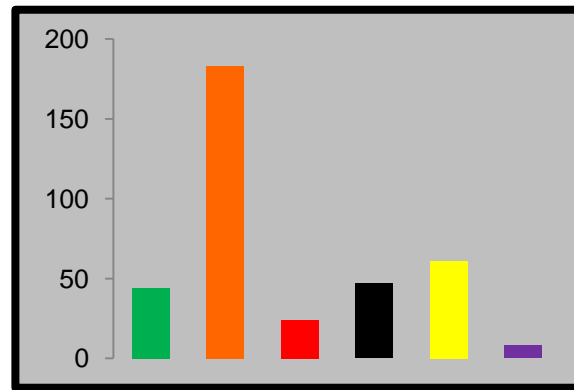
 Not specified

Severity of toxicity

- **Non-hematologic items**



Non-hematologic, nos

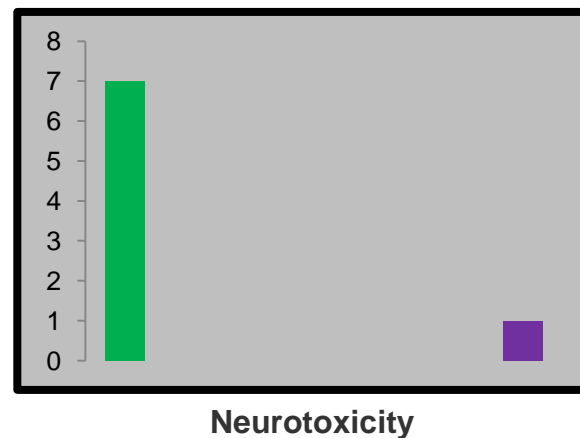
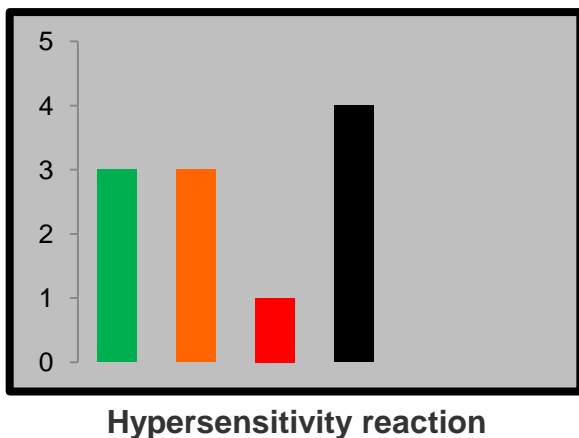
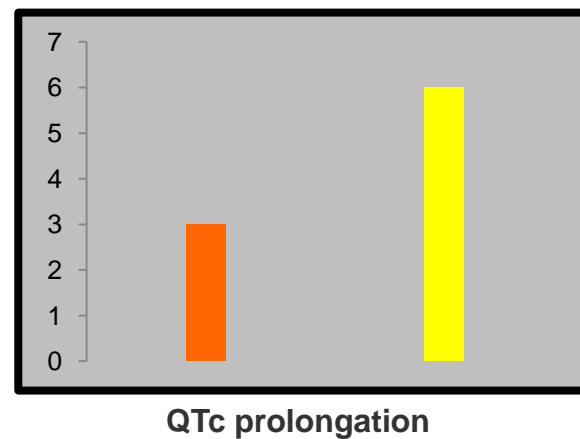
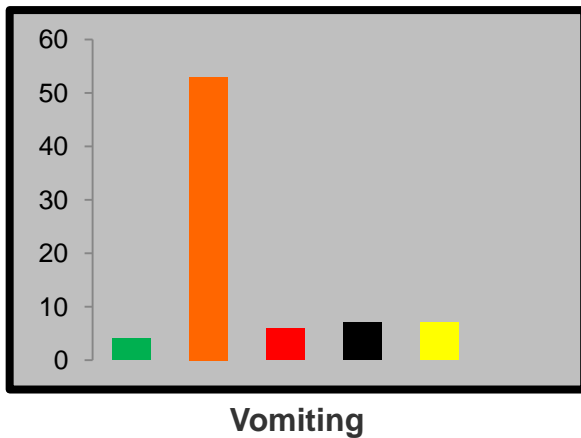


Organ-specific items (all)

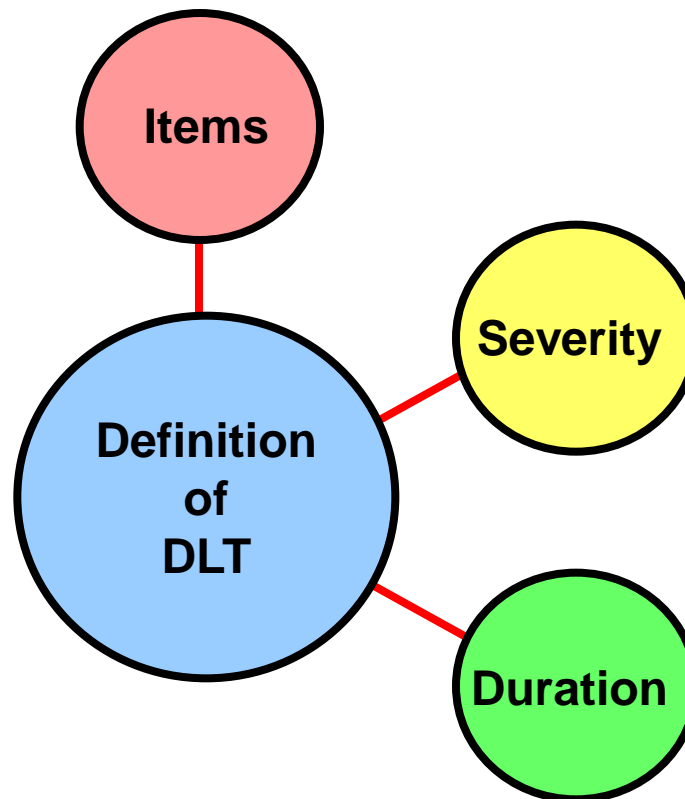


Severity of toxicity

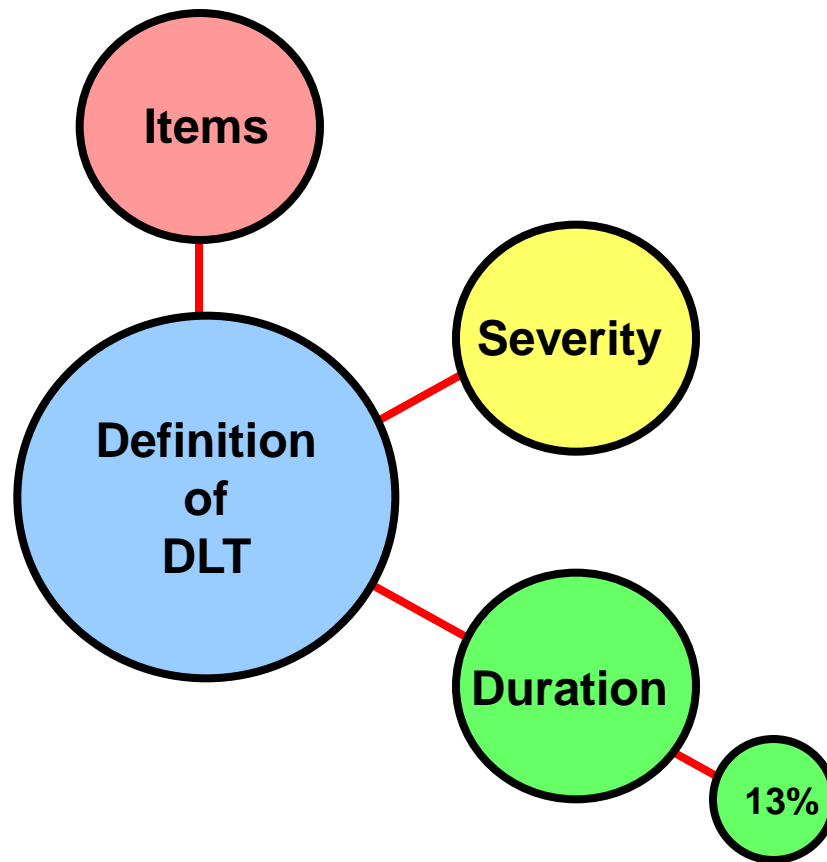
- Organ-specific items



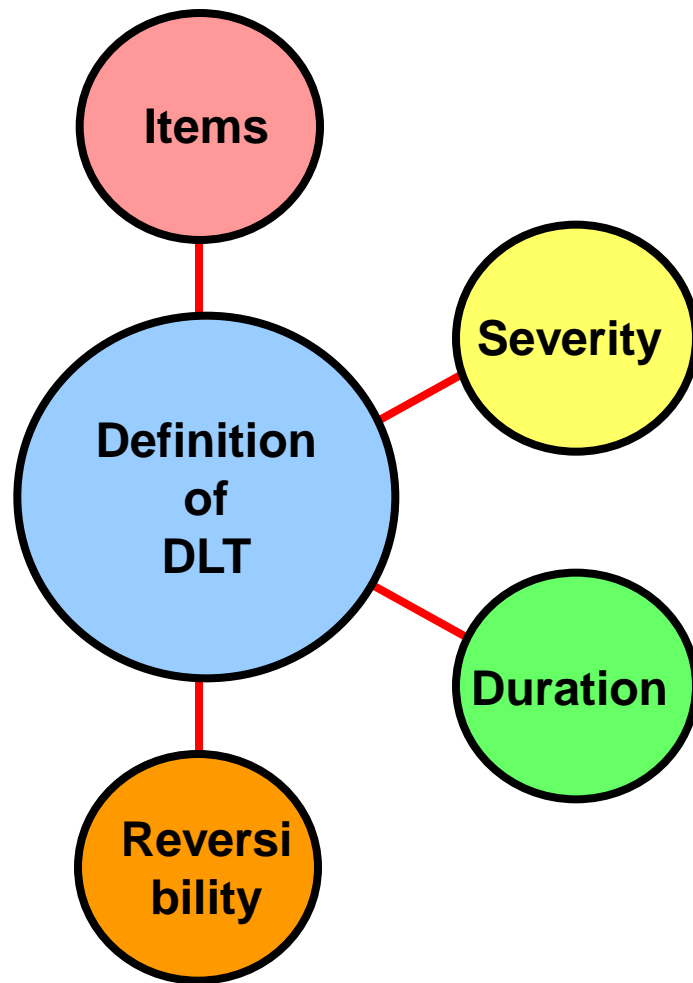
Duration of toxicity



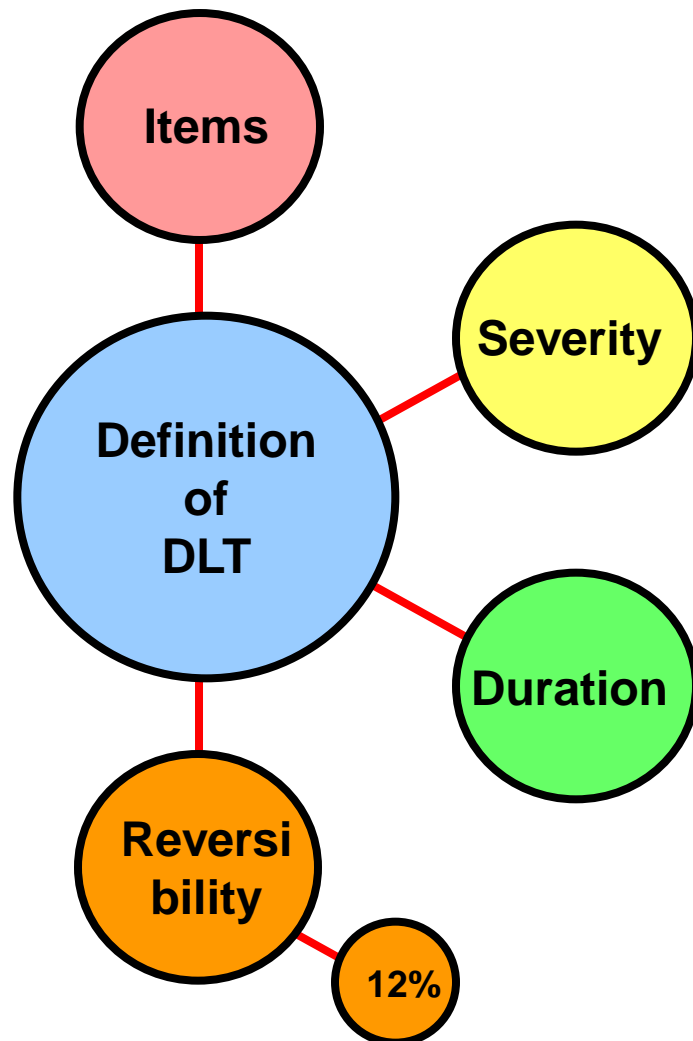
Duration of toxicity



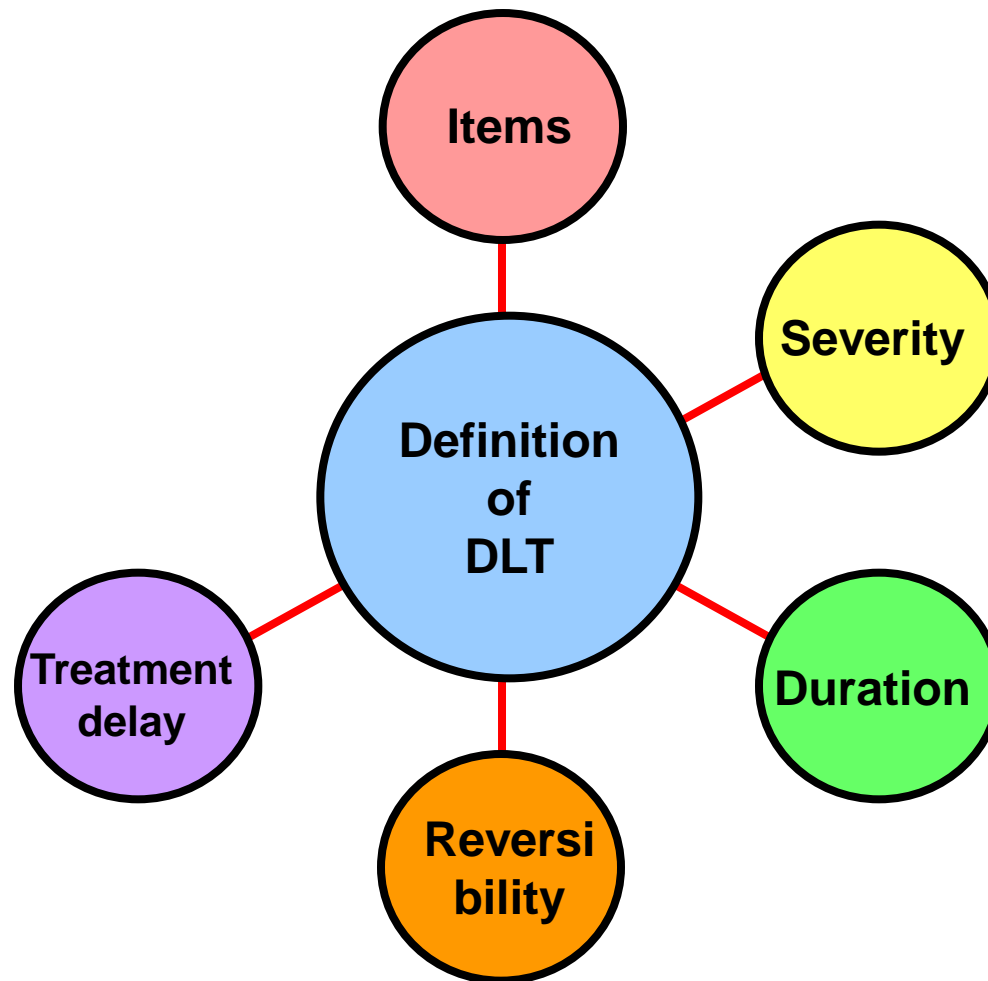
Reversibility of toxicity



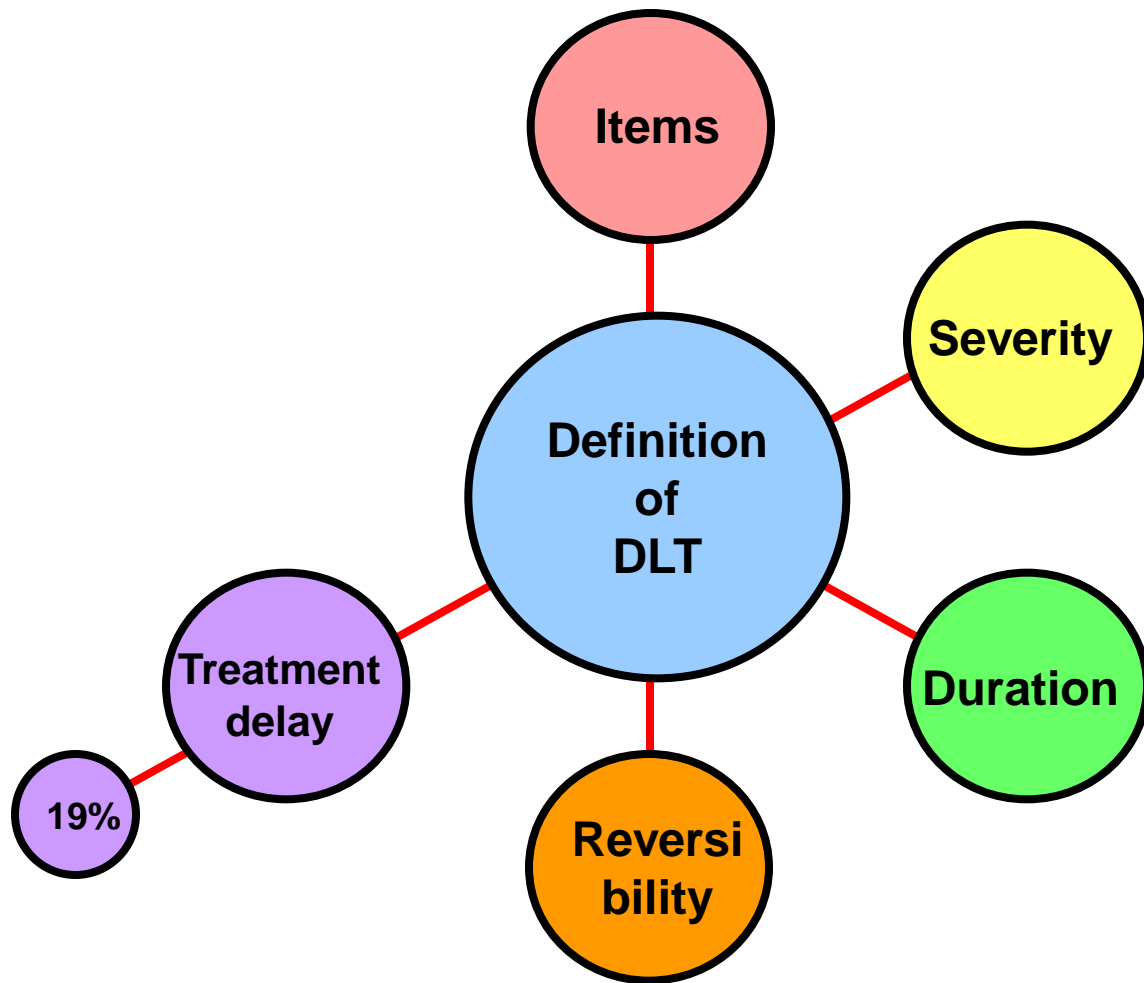
Reversibility of toxicity



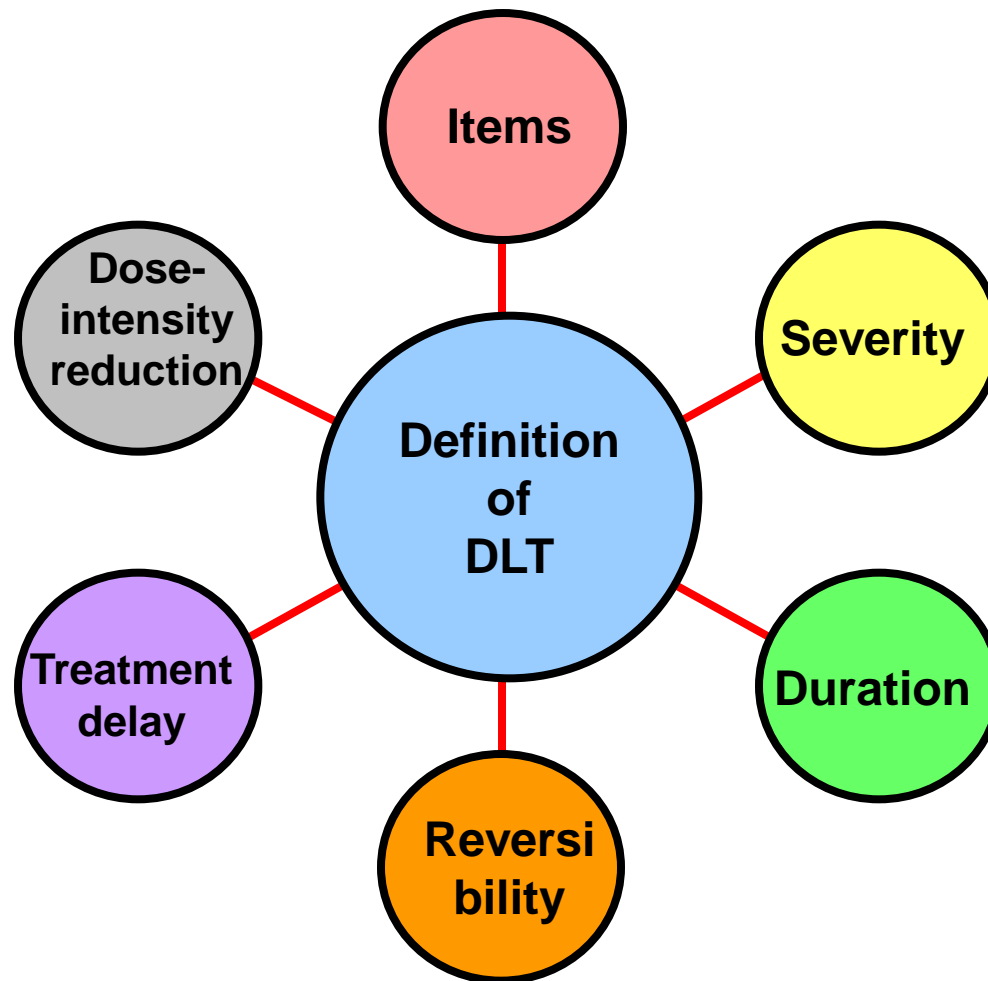
Treatment delay



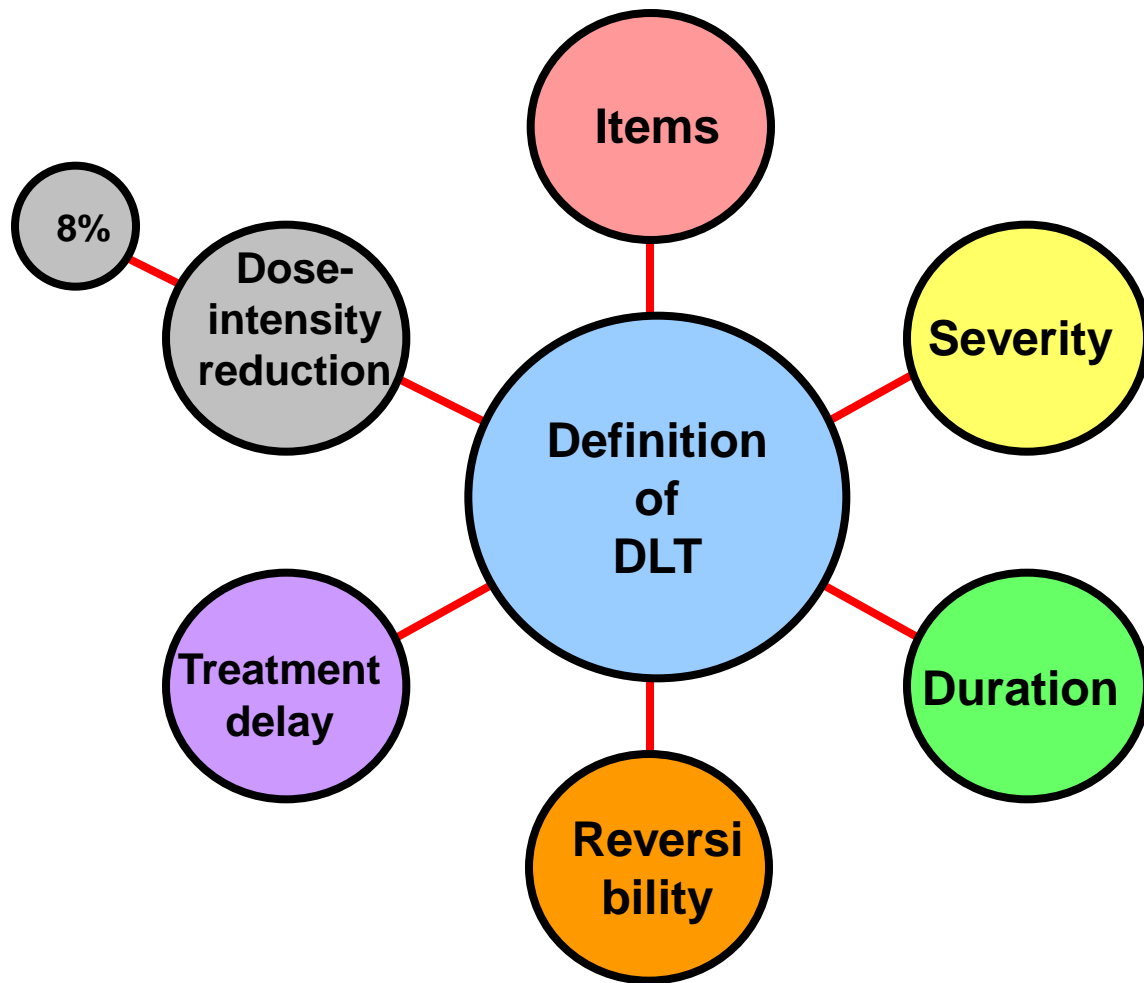
Treatment delay



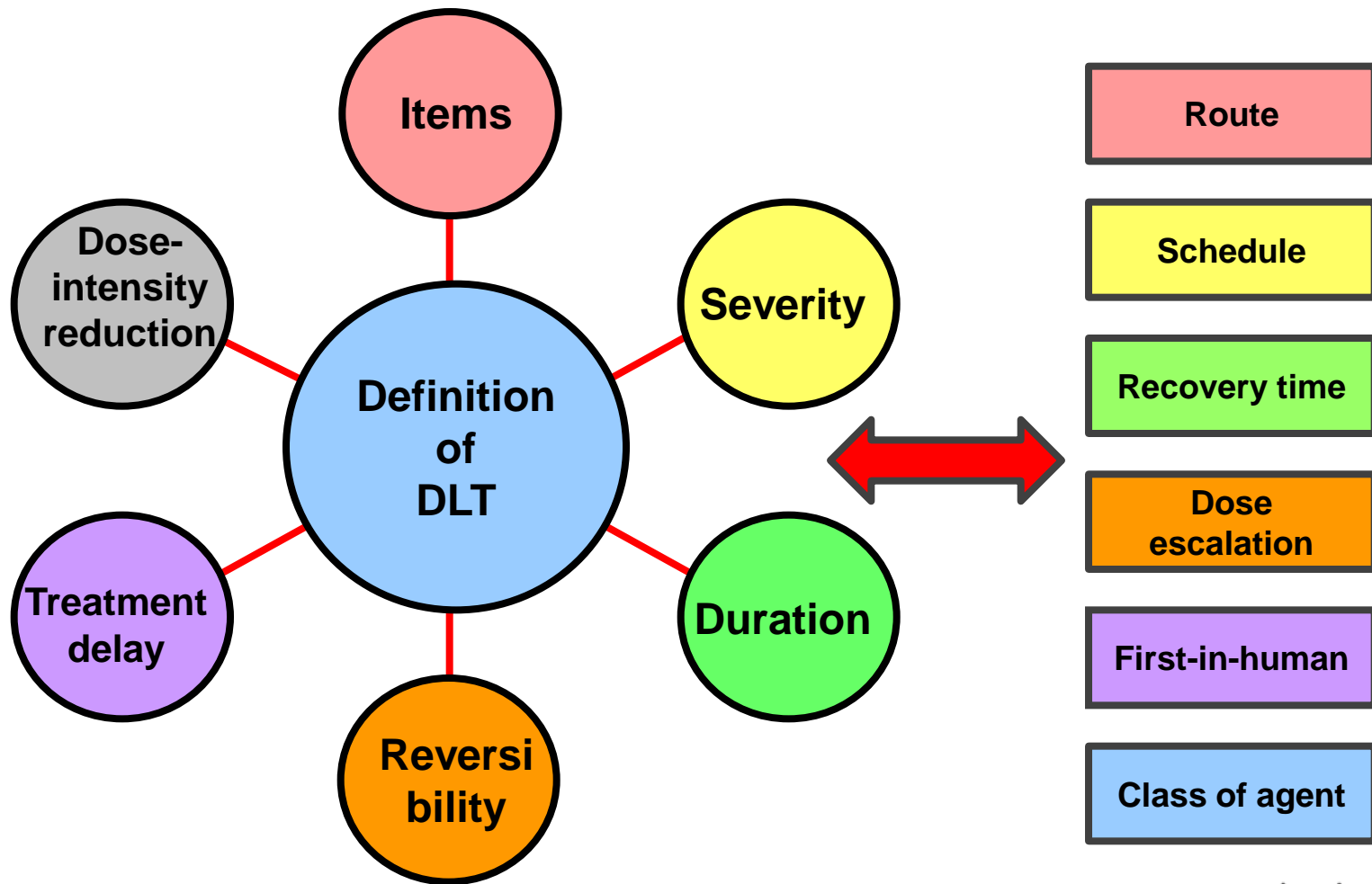
Dose-intensity reduction



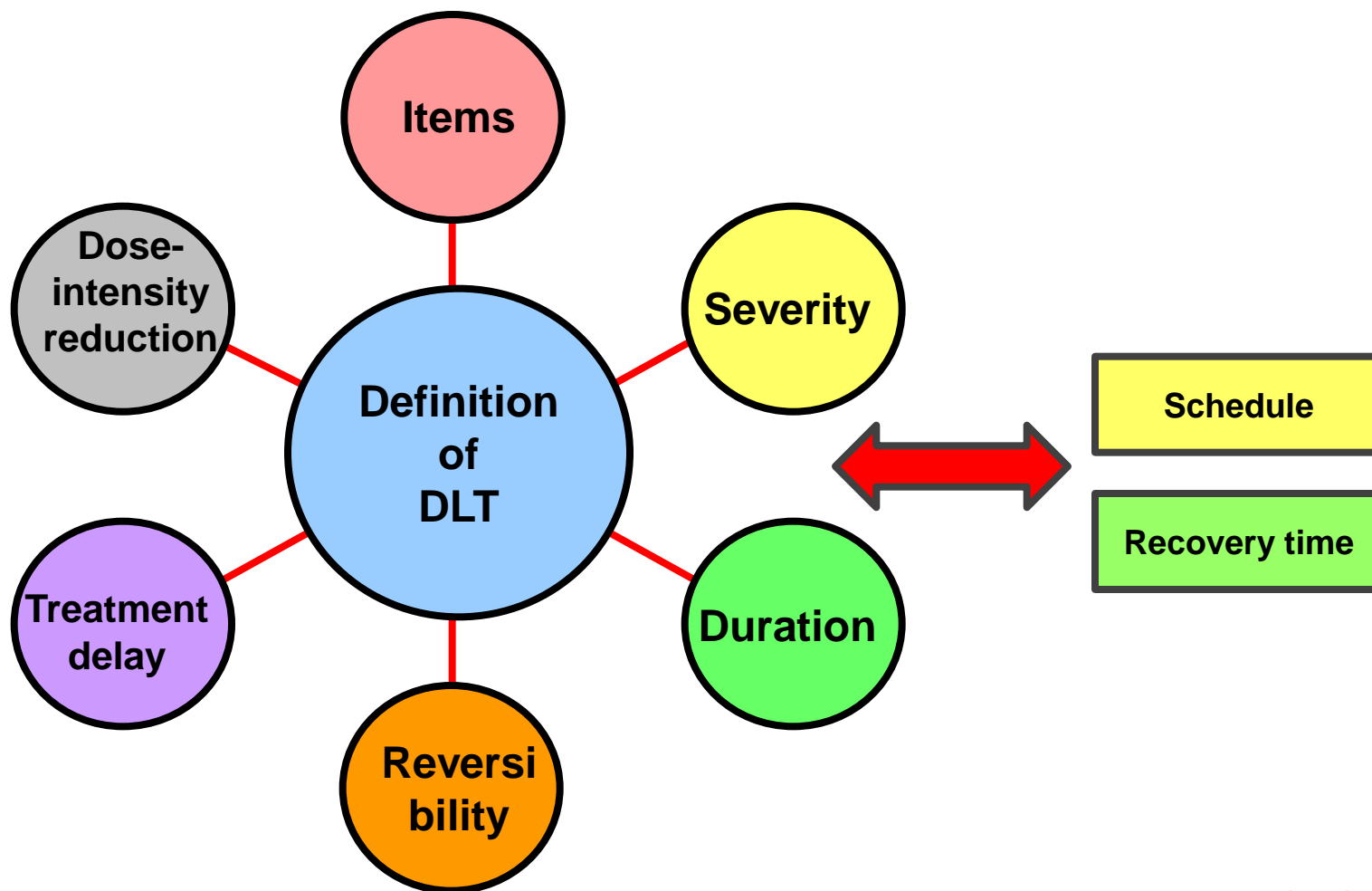
Dose-intensity reduction



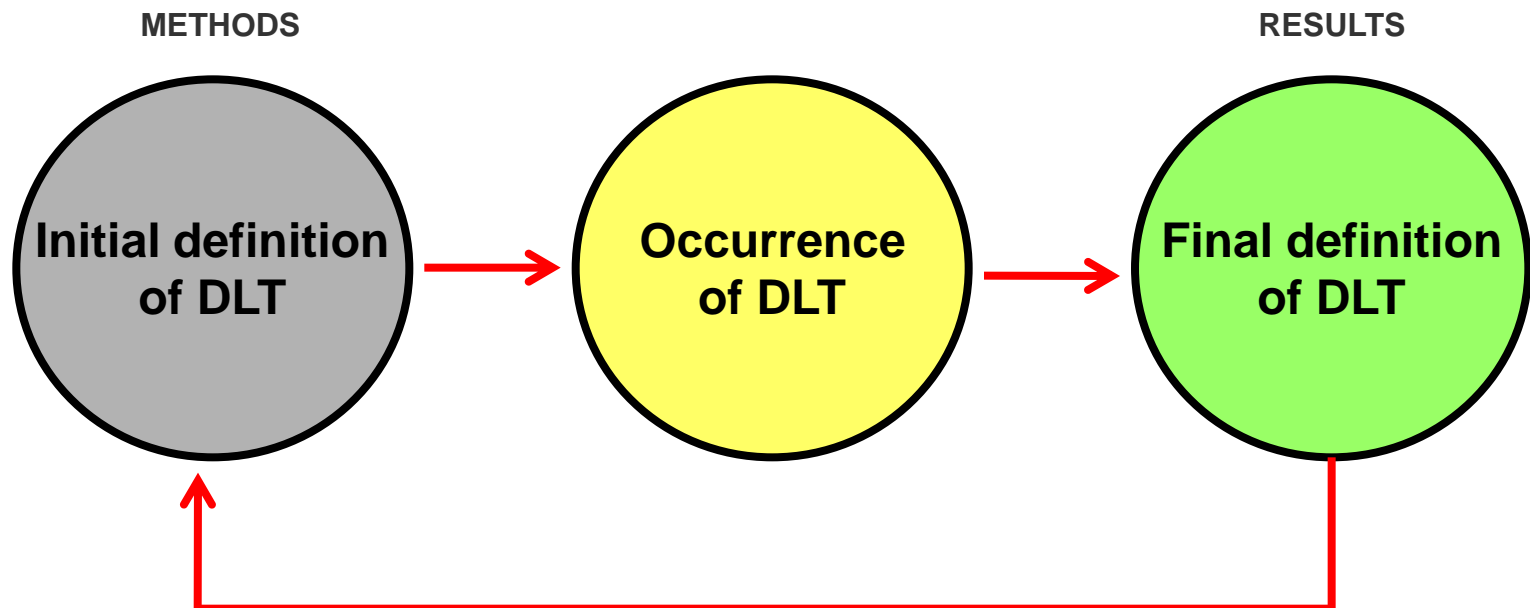
Influencing factors



Influencing factors



Final definition of DLTs



Final definition of DLTs

Proportion of **discrepancies** between the **initial** and the **final** definition of DLT

=

25%

Summary

- **Heterogeneity** of the definition of DLT
- Definition of DLT depends on **drug schedule**
- High rate of **discrepancies** between the initial and the final definition of DLT

Recommendations

