Do we need phase Design for Vaccine Development and When?

FDA Regulation for Drug Development

- Safety
  - Federal Food, Drug, and Cosmetic Act in 1938 (Pub. L. No. 75-717, 52 Stat. 1040)
- Efficacy
  - The Kefauver-Harris Amendments in 1962

Clinical Trials in Drug Development

- Phase 1- Determine a safe dose
- Phase 2- Determine a preliminary efficacy
- Phase 3- Confirm efficacy

Phase 1

- Determine a Maximum Tolerated Dose (MTD)

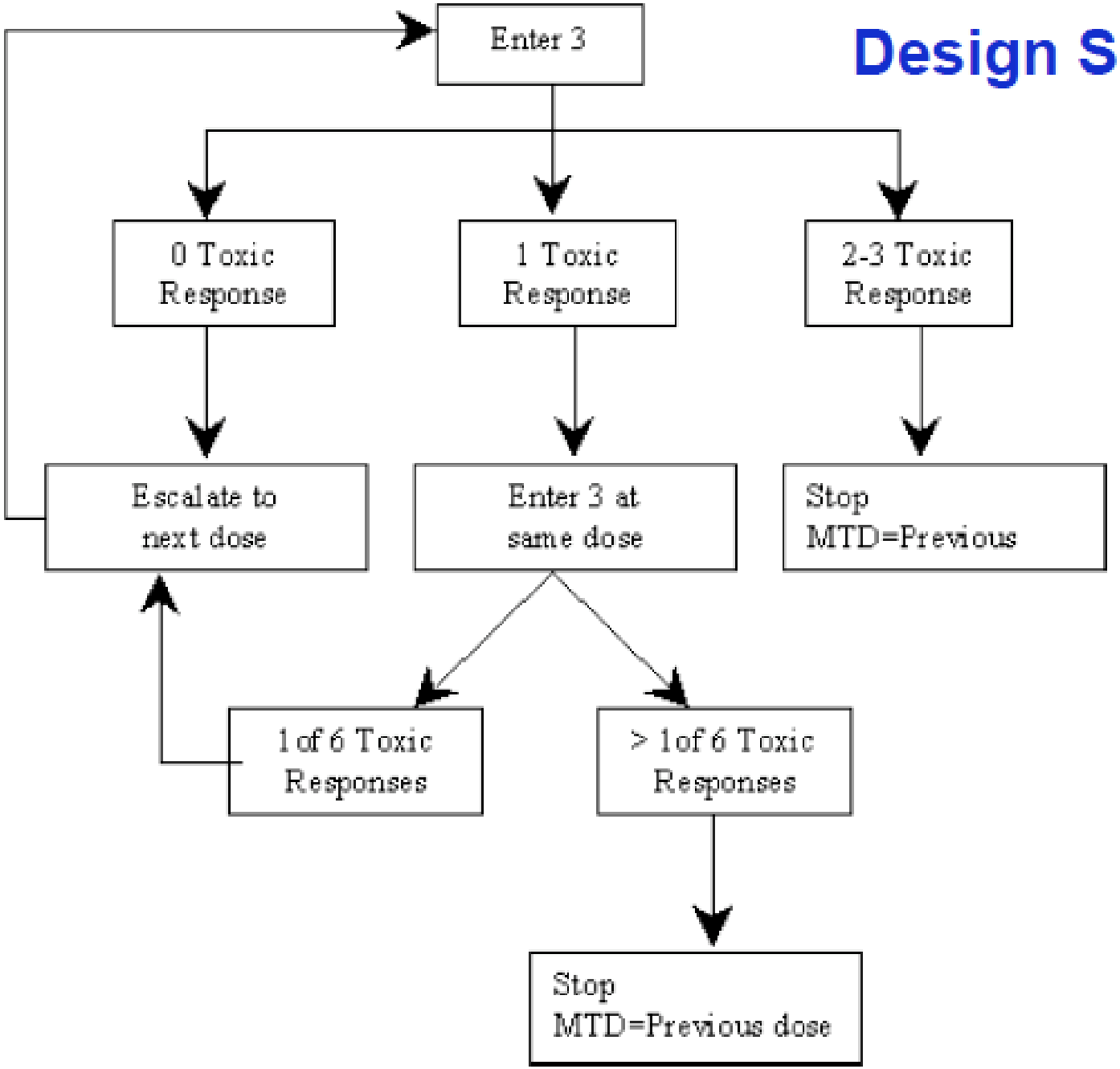
  The highest dose that will produce the desired effect without unacceptable toxicity

- Determine a Biological Active Dose (BAD)

  The dose that will produce the desired effect on a specific molecule’s function

Do we need dose escalation trials in vaccine ?

3 + 3 Phase 1 Study Design Schematic



- Search for cancer vaccine trials on PubMed
- Phase 1, phase1/2, and pilot studies in therapeutic cancer vaccines
- Reported from 1990 through 2011

Are cancer vaccines toxic?

What is the rate of vaccine-related toxicity in relation to the number of vaccinated patients?

Vaccine trials			All Grade 3/4 Toxicities		Systemic Vaccine Related Grade 3/4 Toxicities	
Vaccine Category	**No. Trials**	**No. Patients**	**No. Events**	**%**	**No. Events**	**%**
Autologous	**88**	**1692**	**37**	**2.19**	**23**	**1.36**
DC	58	922	9	0.98	3	0.33
Tumor	30	770	28	3.64	20	2.60
Allogeneic	**17**	**407**	**22**	**5.41**	**5**	**1.23**
Synthetic	**136**	**2853**	**108**	**3.79**	**35**	**1.23**
Peptide	68	1333	40	3.00	11	0.83
DNA	17	311	1	0.32	1	0.32
RNA	2	36	0	0	0	0
Virus	31	662	23	3.47	13	1.96
Bacteria	6	126	27	21.43	7	3.97
Anti-idiotypic	10	362	15	4.14	0	0
Liposomal	2	23	2	8.70	2	8.70
TOTAL	**241**	**4952**	**167**	**3.37**	**62**	**1.25**

What is the rate of vaccine-related toxicity in relation to the number administered vaccines?

Vaccine Trials				All Grade 3/4 Toxicities		Systemic Vaccine Related Grade 3/4 Toxicities	
Vaccine Category	**No. Trials**	**No. Patients**	**No. Vaccines**	**No. Events**	**%**	**No. Events**	**%**
Autologous	**73**	**1301**	**5722**	**20**	**0.35**	8	**0.14**
DC	51	796	3424	9	0.26	3	0.09
Tumor	22	505	2298	11	0.48	5	0.22
Allogeneic	**16**	**347**	**1874**	**22**	**1.17**	**5**	**0.26**
Synthetic	**117**	**2376**	**14239**	**78**	**0.55**	**30**	**0.21**
Peptide	61	1183	7637	37	0.48	9	0.12
DNA	15	259	1388	1	0.07	1	0.07
RNA	2	36	335	0	0	0	0
Virus	27	535	2365	22	0.93	13	0.55
Bacteria	4	80	530	9	1.70	5	0.94
Anti-idiotypic	7	266	1938	7	0.36	0	0
Liposomal	1	17	46	2	4.35	2	4.35
TOTAL	**206**	**4024**	**21835**	**120**	**0.55**	**43**	**0.20**

Does dose escalation determine MTD?

Vaccine Category	No. Trials	No. Patients	Grade 3/4			Trials with DLT
			No. Trials	No. AE	No. *Related AE	
Autologous	**40**	**847**	**2**	**11**	**8**	**0**
DC	27	466	0	0	0	0
Tumor	13	381	2	11	8	0
Allogeneic	**5**	**130**	**3**	**20**	**5**	**1**
Synthetic	**83**	**2008**	**17**	**67**	**27**	**2**
Peptide	36	852	7	10	7	0
DNA	12	208	1	1	1	0
Virus	26	592	7	47	17	0
Bacteria	4	81	4	27	7	2
Anti-idiotypic	8	339	1	7	0	0
Liposomal	1	17	1	2	2	0
TOTAL	**127**	**2985**	**22**	**98**	**40**	**3**

Trials with DLT

Trial	Vaccine	Toxicity	DLT
Dols et al. 2003	Allogeneic HER2/neu(+) breast cancer cells (SC) with GM-CSF or BCG	Nausea/Vomiting	1 patient at 250 µg/m2 GM-CSF
Maciag et al. 2009	*L. monocytogenes* secreting HPV-16 E7 fused to *Lm* listeriolysin O (IV)	Hypotension	3 patients at highest dose level
Guthmann et al. 2004	GM3 ganglioside with *N. meningitidis* outer membrane (IM)	Hypotension	1 patient at highest dose level

Conclusion

- Dose escalation design has no role in defining
  - The maximum tolerated dose (MTD)
  - Except for bacterial vector vaccines

Does dose escalation determine BAD?

Vaccine Category	No. Trials	Dose Related Cellular Immune Response
Autologous	32	0
Allogeneic	4	0
Synthetic	80	0
Total	116	0

Conclusion

- Dose escalation design has not been shown to define
  - Tolerability (except for bacterial vector vaccines)
  - Biologically active dose (BAD)

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A new design paradigm is needed

Alternative Clinical Trial Design For Cancer Vaccine

Step 1. Determining a starting dose of a vaccine

Vaccine class that is used before & found to be toxic (e.g., bacterial vector) → Proceed to traditional phase 1 trial

Vaccine class that is used before & found to be non-toxic (e.g., peptide) → Use Immune Active Dose (IAD) from previous clinical trials

Vaccine class that is not used before & not expected to be toxic → One Patient Escalation Design (OPED)

- One patient per tested dose is treated until an immune response is induced (IAD).
- Then expand that dose level, one patient at a time, until achieving an additional immune response.
- If no additional immune response in 7 patients, stop adding patients and continue escalation of one patient at a time.

Step 2. Combination Design "Vaccine + X"
(X is an immune modulator, chemotherapy or targeted agent)

X had no DLT	X had a DLT	X' DLT is unknown
↓	↓	↓
Use the same dose	Use the dose below MTD	Proceed to traditional phase 1

How do we determine a starting dose of a vaccine?

Determining a starting dose of a vaccine

Class used before &
NON-TOXIC
(e.g., peptide)

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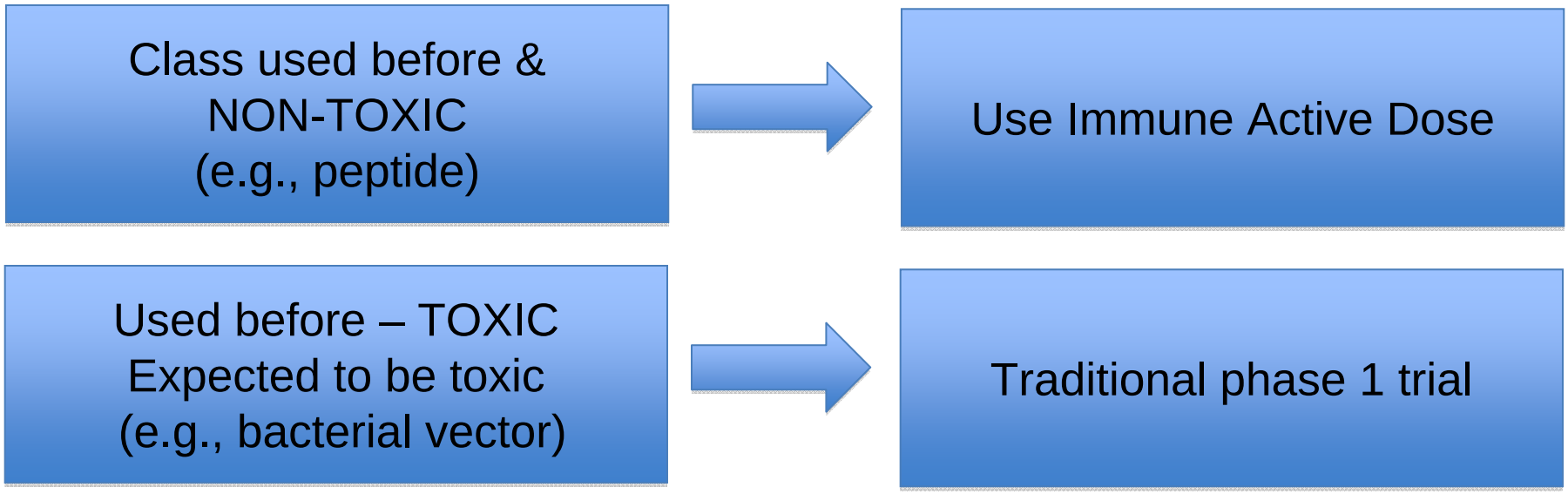
Used before – TOXIC
Expected to be toxic
(e.g., bacterial vector)

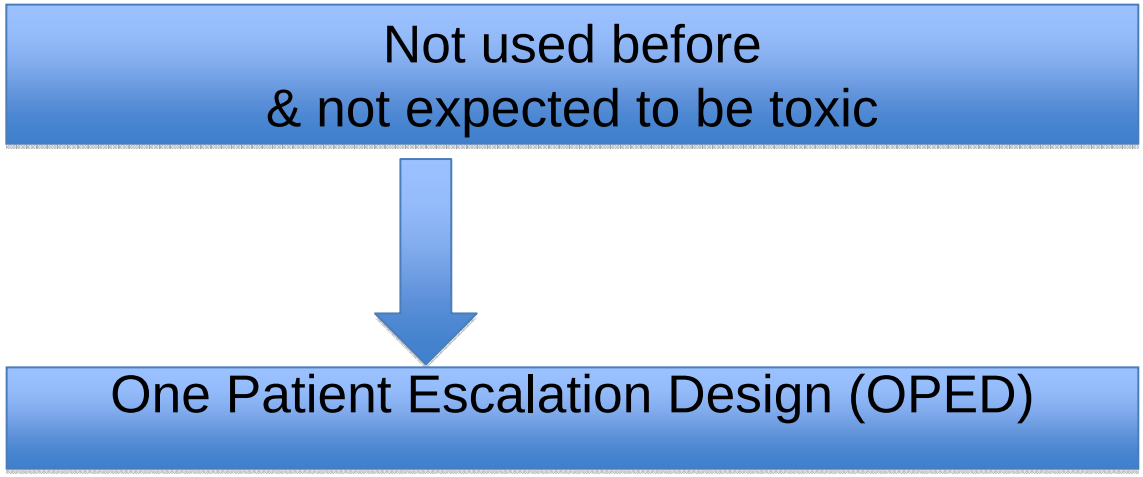
Determining a starting dose of a vaccine



Determining a starting dose of a vaccine

Not used before
& not expected to be toxic

Determining a starting dose of a vaccine



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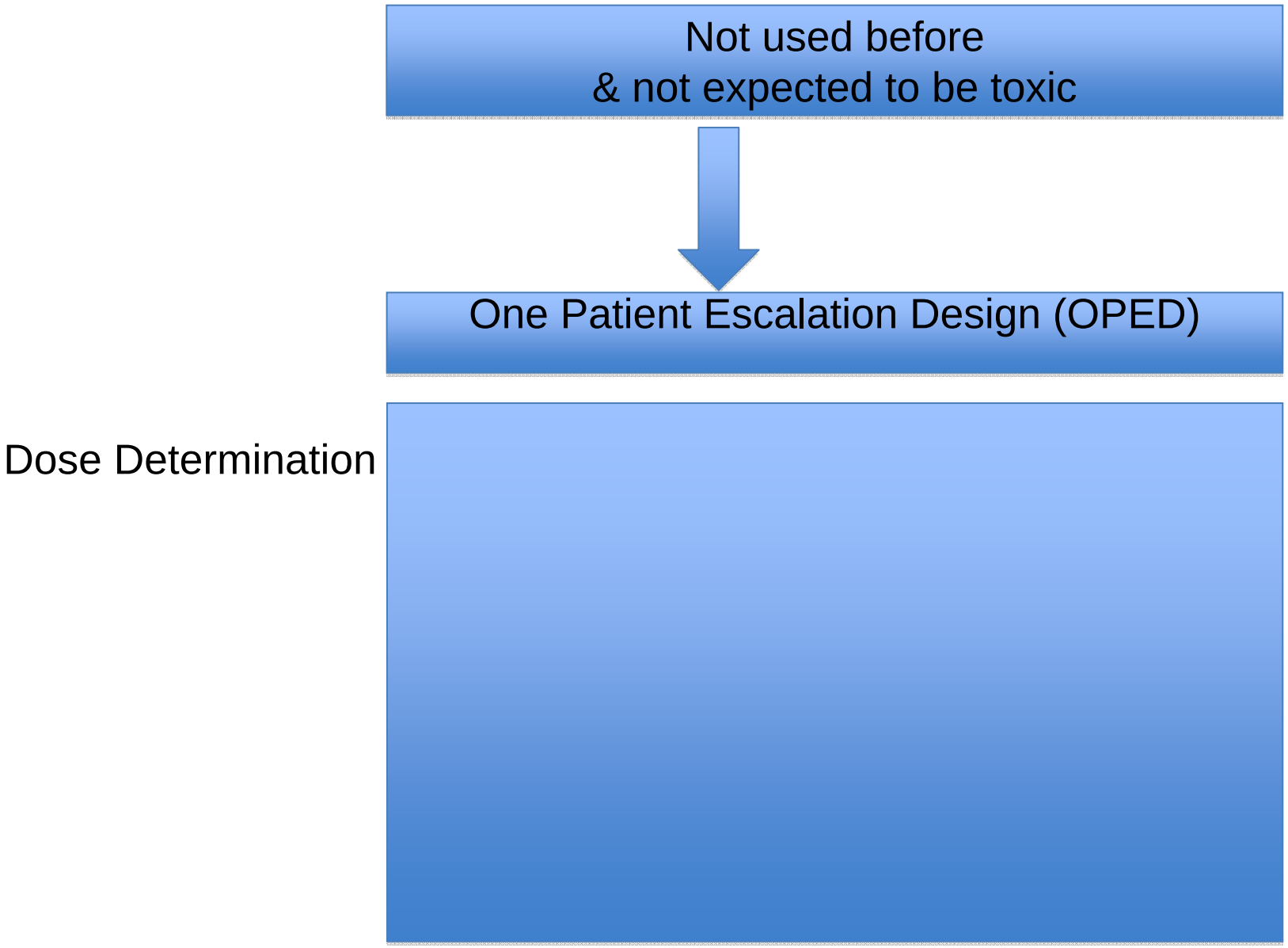

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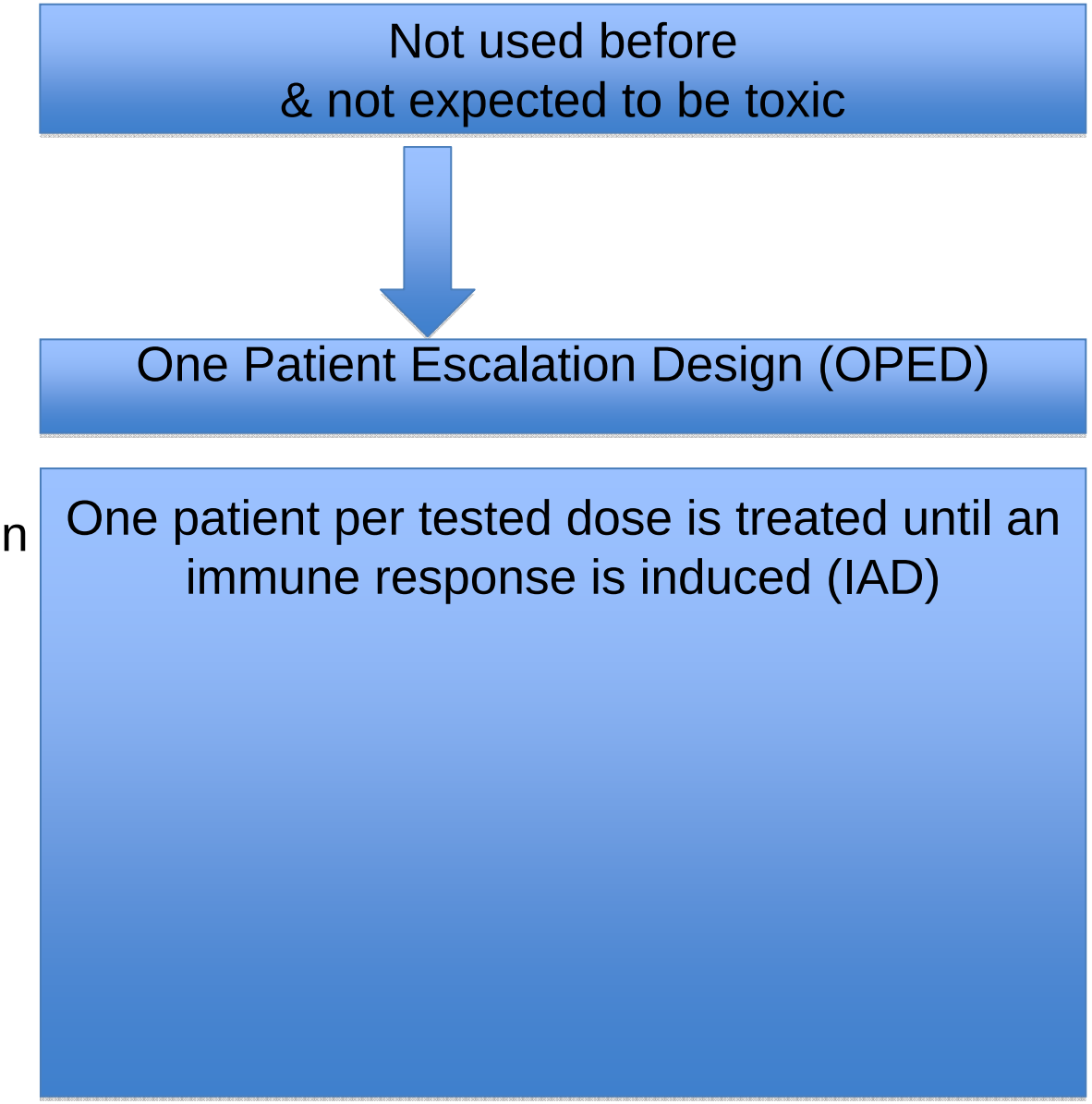

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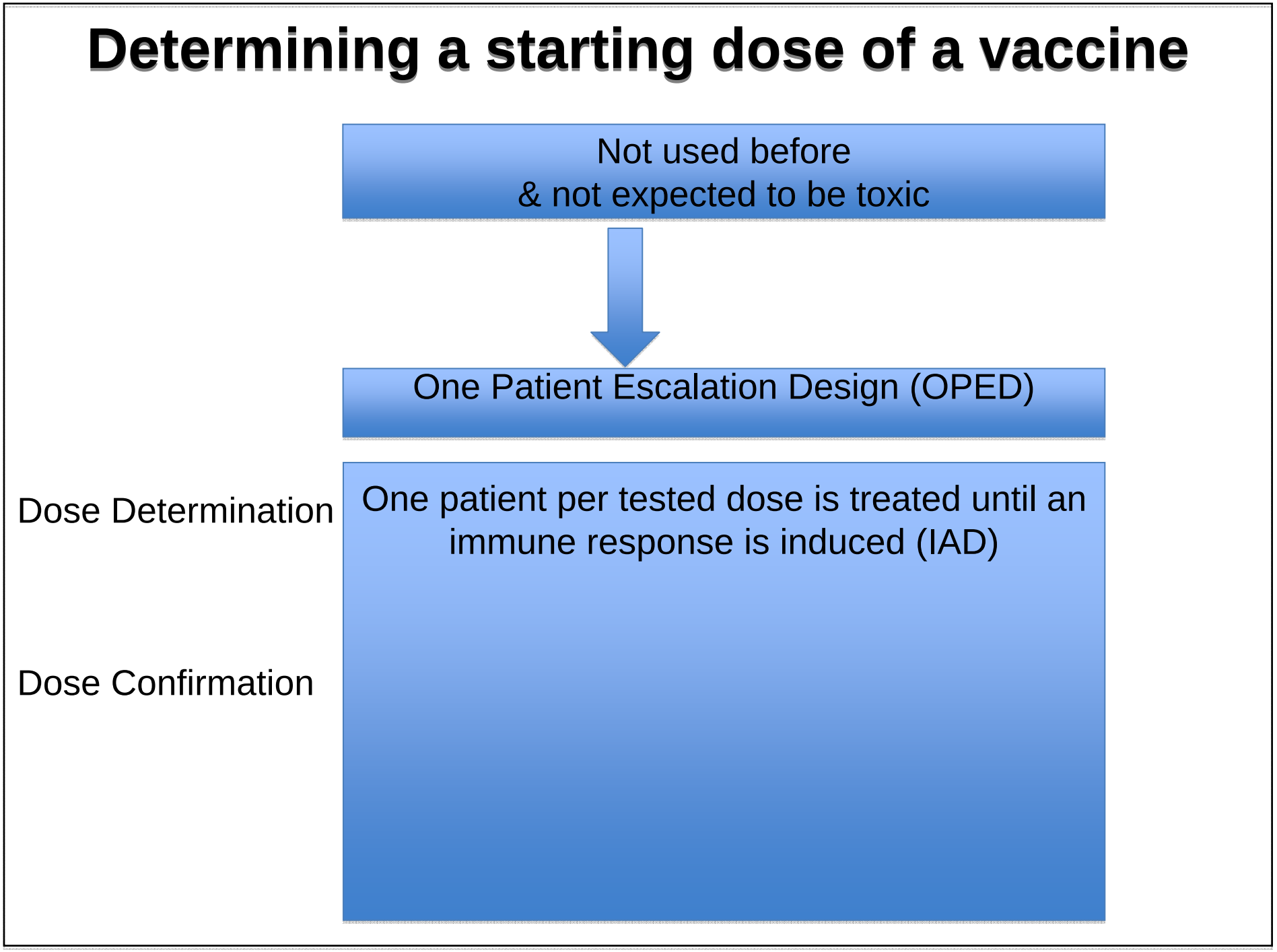

Determining a starting dose of a vaccine

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One Patient Escalation Design (OPED)

Dose Determination

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Dose Confirmation

Expand IAD one patient at a time up to 7 pts until achieving an additional immune response

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