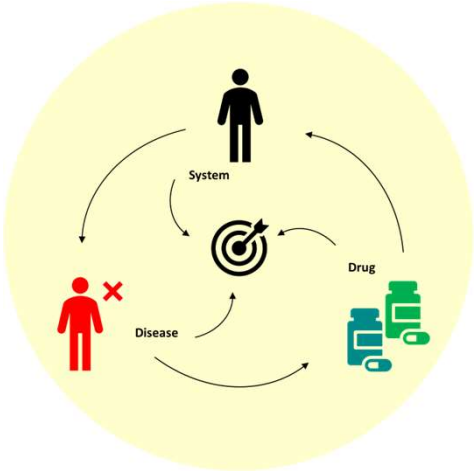

From physiology to disease: A quantitative framework for system-disease-drug interaction in cortisol replacement therapy

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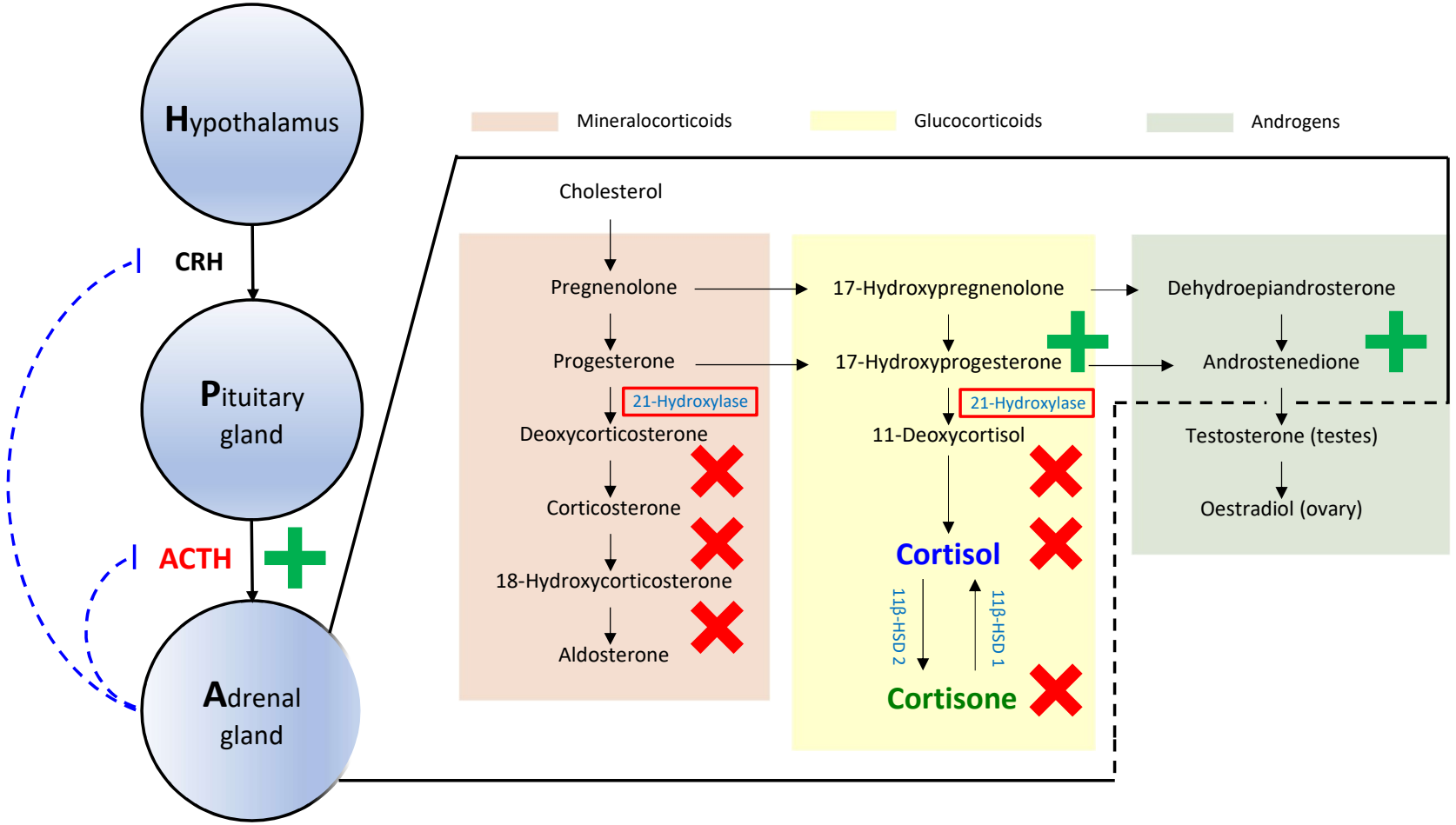
32nd PAGE meeting - Dose extrapolation & posology
Rome, 27 June 2024

Why do we need cortisol replacement therapy?



Healthy state:

- Production following circadian rhythm
- Feedback inhibition maintaining system homeostasis

Disease - congenital adrenal hyperplasia (CAH):

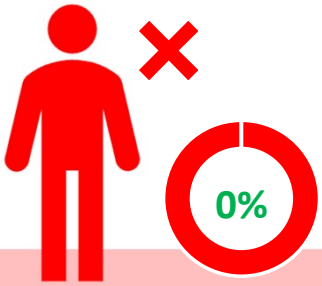
- Reduced 21-hydroxylase activity
- Reduced cortisol production
- Reduced feedback inhibition
- ACTH and androgens overproduction

ACTH: Adrenocorticotropic hormone
CRH: Corticotropic releasing hormone

Merke et al., Lancet (2005)
Claahsen-van der Grinten et al., Endocrine Reviews (2022)

Disease severity depends on enzymatic activity

SW



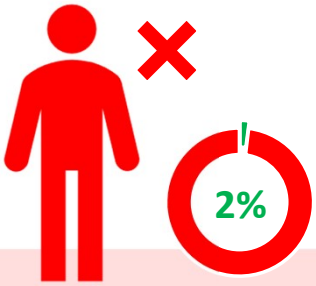
Enzymatic activity

Cortisol deficiency

Electrolyte imbalances

Signs of androgen excess from early life

SV



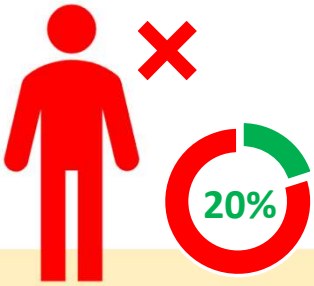
Enzymatic activity

Milder cortisol deficiency

Milder electrolyte imbalances

Signs of androgen excess from early life

NC



Enzymatic activity

Often asymptomatic

Signs of androgen excess later in life

SW: Salt wasting
SV: Simple virilising
NC: Non-classic

Merke et al., Lancet (2005)
Claahsen-van der Grinten et al., Endocrine Reviews (2022)

Challenges of cortisol replacement therapy

IR

10-15 mg/m^2/day

Divided in 3-4 doses:
Throughout day

MR

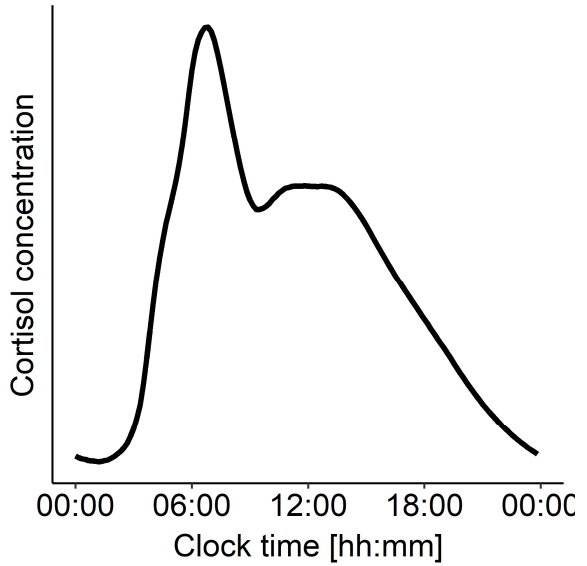
10-15 mg/m^2/day

Divided in 2 doses:
Before sleep and at waking

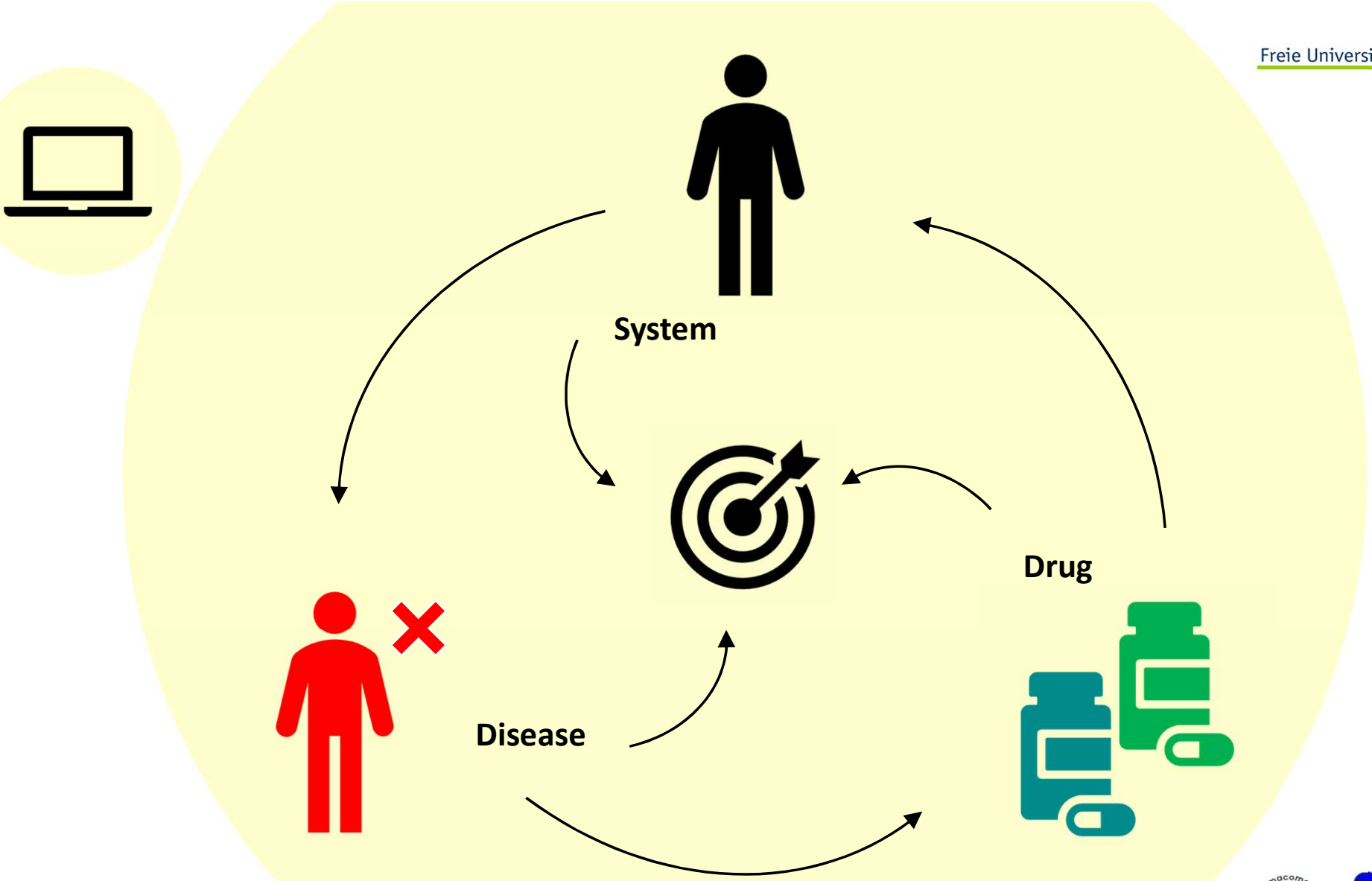
Therapeutic goals:

Mimicking cortisol physiological circadian profiles

Avoiding hormonal imbalances



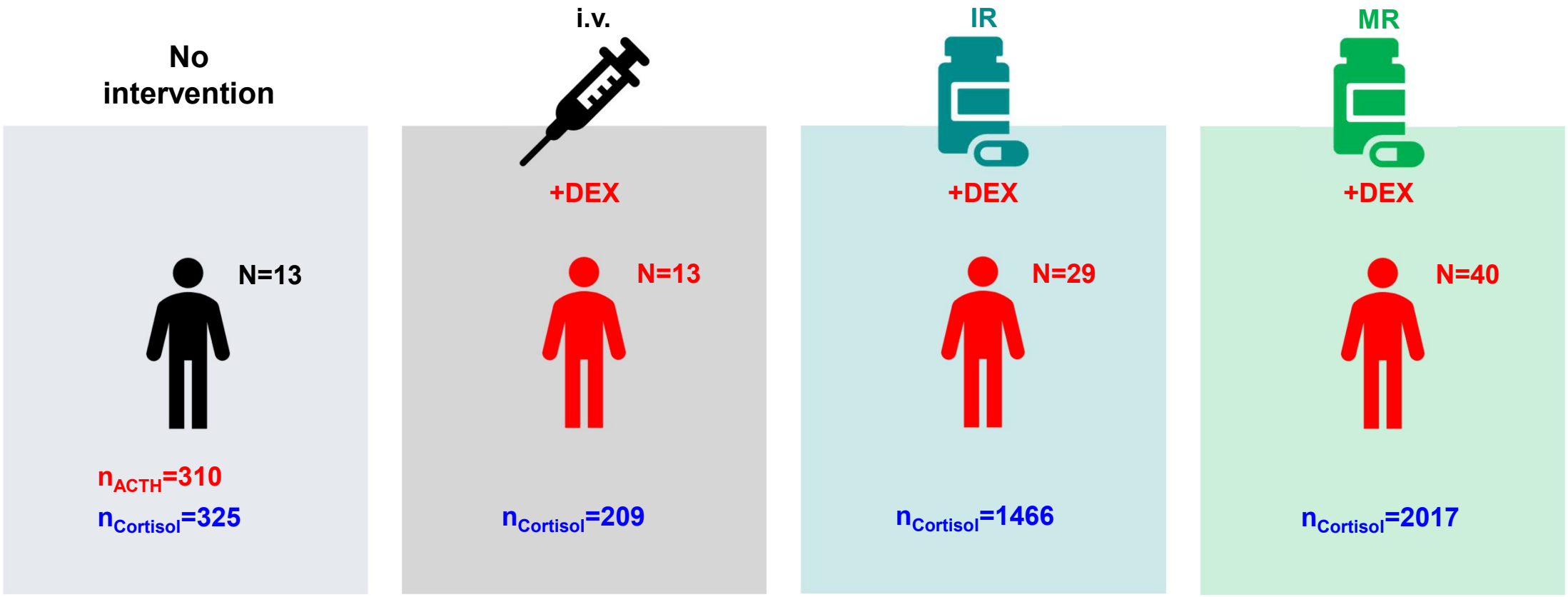
IR: Immediate-release
MR: Modified-release


System
Drug
Disease

Healthy volunteers clinical trial data

Freie Universität Berlin

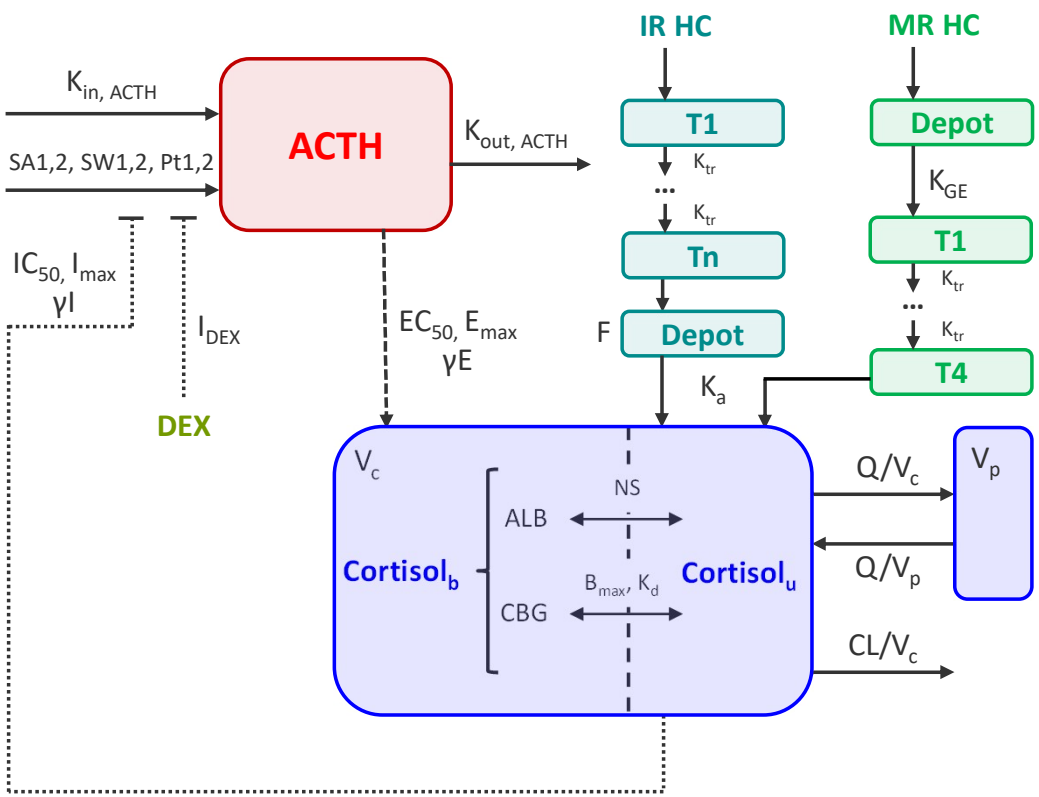
University of Sheffield



IR: Immediate-release
MR: Modified-release
DEX: Dexamethasone
N: Number of participants
n: Number of samples :

CLINICAL PHARMACY

Developed framework: How does it work?



Pulsatile secretion modelled using **surge functions**:
Estimated **morning peak** time **~06:00**

Production rate **dependent on ACTH** concentration:
E_{max}=5400 nmol/L, **EC_{50}=6.63 pmol/L**, γE=2.94

Feedback **inhibition** on **ACTH** pulsatile secretion:
I_{max}=100%, **IC_{50}=160 nmol/L**, γI=5.33

Transit compartment absorption model
Bioavailability=34.4%

Gastric emptying model using step function followed by **4 transit** compartments
Bioavailability =33.8%

IR: Immediate-release
MR: Modified-release
HC: Hydrocortisone

Developed framework: How did we apply it?

Evaluate impact of disease:

Assuming E_{max} represents enzymatic activity

SW
E_{max}=0%

SV
E_{max}=2%

NC
E_{max}=20%

Simulate ACTH and cortisol concentrations, compare to healthy

CAH: Congenital adrenal hyperplasia
SW: Salt wasting
SV: Simple virilising
NC: Non-classic

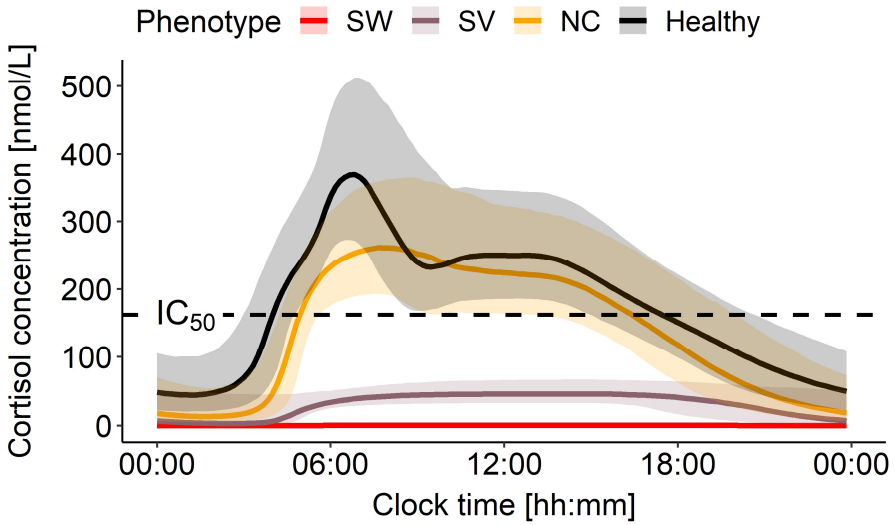
Simulated profiles approximate clinical phenotypes

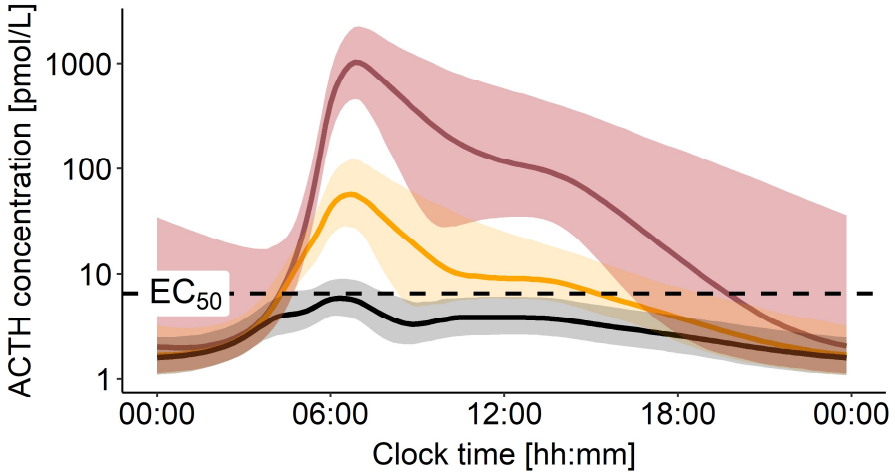
SW
E_{max}=0%

SV
E_{max}=2%

NC
E_{max}=20%

Healthy
E_{max}=100%





SW and **SV**:
Negligible cortisol concentrations

NC:
Similar profiles to healthy throughout all day

SW and **SV**:
Morning peak ACTH concentration >100-fold higher than healthy

NC:
Morning peak ACTH concentration ~10-fold higher than healthy

CAH: Congenital adrenal hyperplasia
SW: Salt wasting
SV: Simple virilising
NC: Non-classic

Developed framework: How did we apply it?

Evaluate impact of disease:

Assuming E_{max} represents enzymatic activity

SW
E_{max}=0%

SV
E_{max}=2%

NC
E_{max}=20%

Simulate ACTH and cortisol concentrations, compare to healthy

Evaluate impact of therapy:

SW

NC

Dosing time

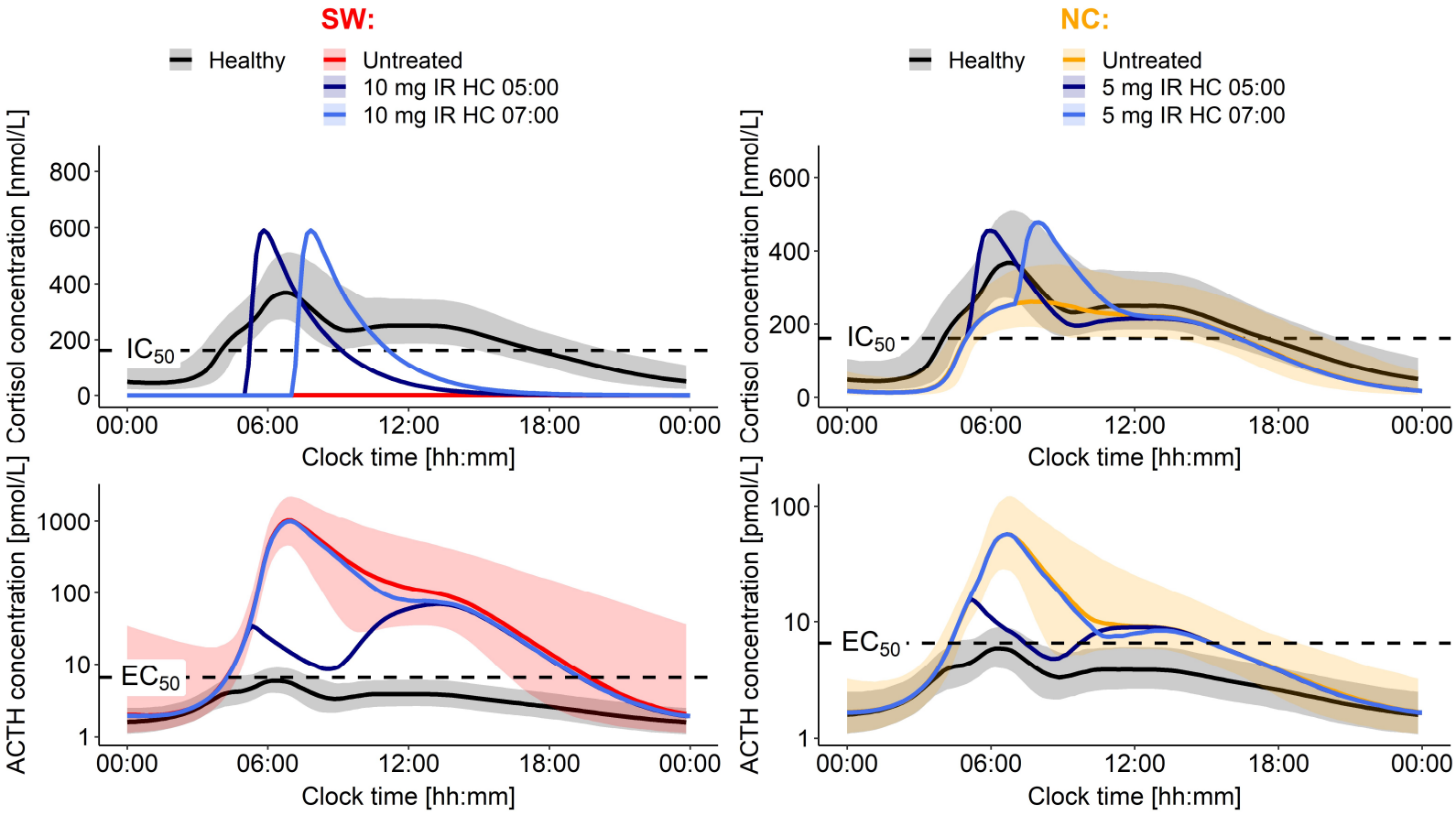
05:00 *vs* 07:00

Simulate ACTH and cortisol concentrations, compare to untreated patients and healthy

CAH: Congenital adrenal hyperplasia
SW: Salt wasting
SV: Simple virilising
NC: Non-classic

IR: Immediate-release
MR: Modified-release

Dosing time is key to regulate system



SW: IR HC fails to mimic well healthy cortisol profiles

Dosing at **07:00** results in **ACTH** overproduction **as untreated patients**

Dosing at **05:00 reduces** morning peak **ACTH** concentration by ~30-fold in **SW** ~5-fold in **NC**

SW: Salt wasting
NC: Non-classic

IR: Immediate-release
HC: hydrocortisone

Developed framework: How did we apply it?

Evaluate impact of disease:

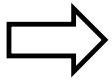
Assuming E_{max} represents enzymatic activity

SW
E_{max}=0%

SV
E_{max}=2%

NC
E_{max}=20%

Simulate ACTH and cortisol concentrations, compare to healthy



Evaluate impact of therapy:

SW

NC

Dosing time

05:00 *vs* 07:00

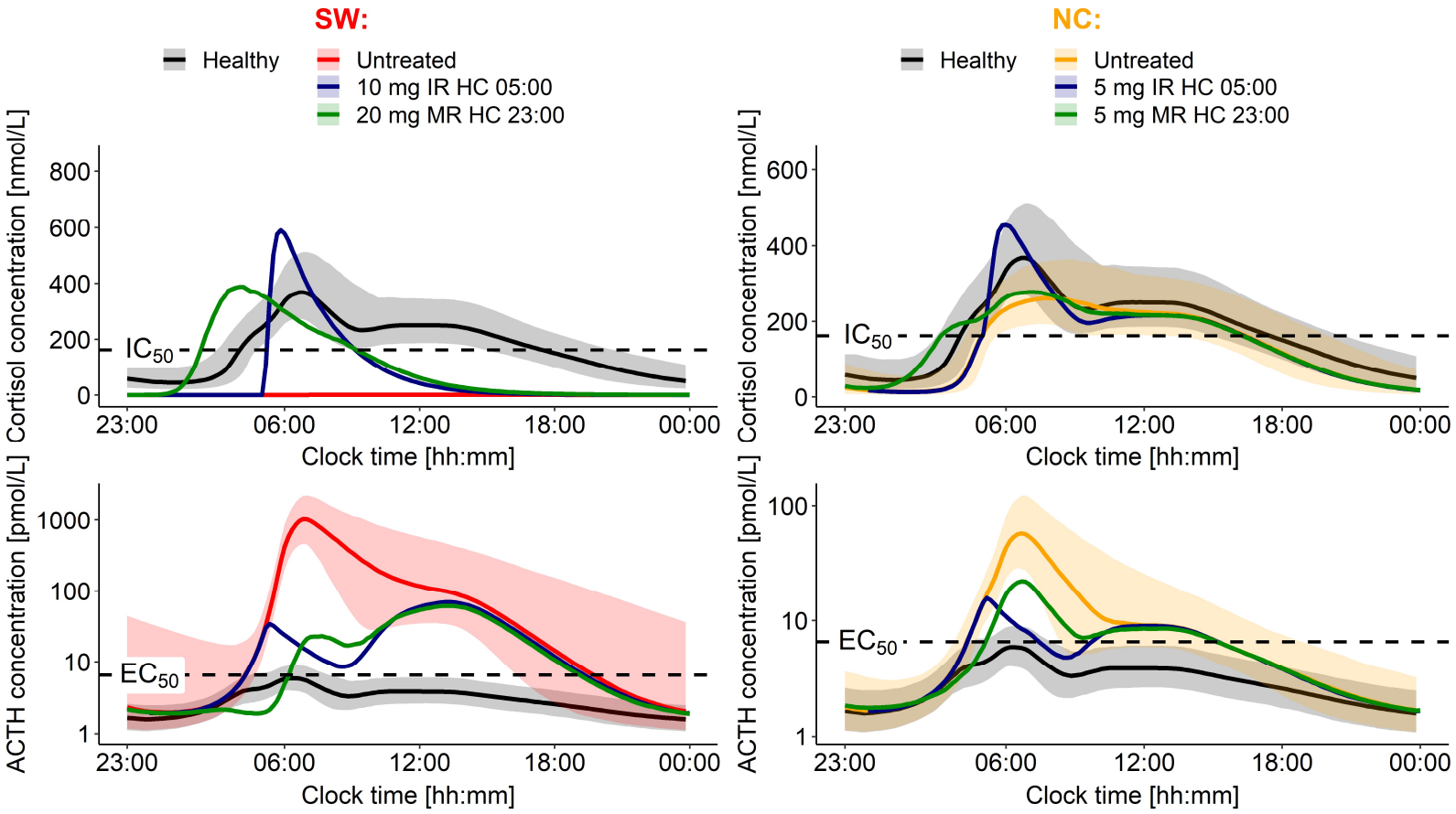
Formulation

IR *vs* MR

Simulate ACTH and cortisol concentrations, compare to untreated patients and healthy

CAH: Congenital adrenal hyperplasia
SW: Salt wasting
SV: Simple virilising
NC: Non-classic
IR: Immediate-release
MR: Modified-release

Most beneficial formulation depends on disease severity



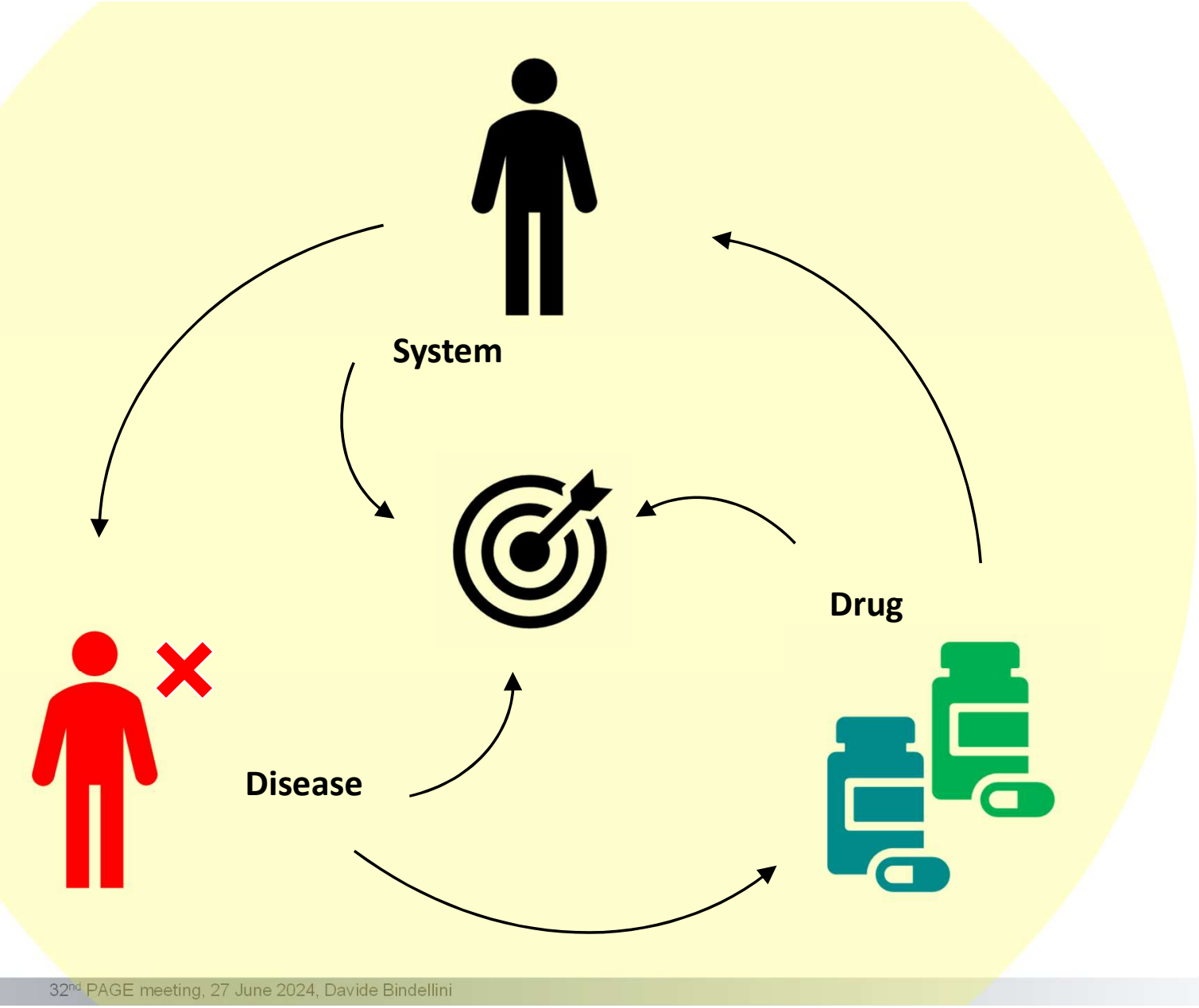
MR HC better mimics healthy cortisol profiles in **SW**

Higher potential to improve system regulation

No large differences between effect of IR and MR in **NC**

SW: Salt wasting
NC: Non-classic

IR: Immediate-release
MR: Modified-release
HC: hydrocortisone



Characterised key processes in **healthy** ACTH-cortisol **system**

Characterised **impact of disease** on system

Approximated CAH patients' clinical phenotypes

Characterised IR and MR **HC PK** and **interaction** with diseased **system**

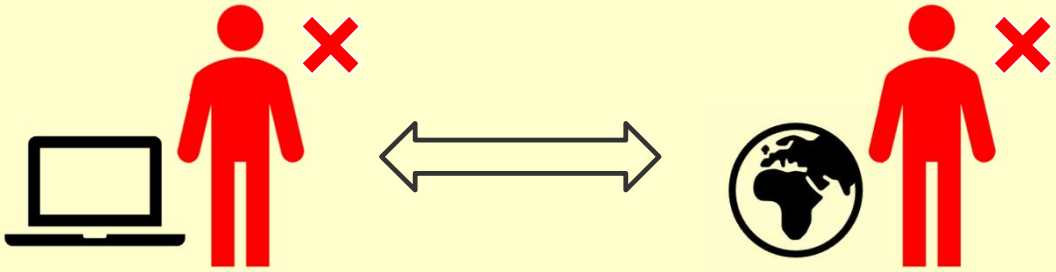
Importance of dosing time

Most beneficial formulation varies per patient type

Individualised therapy to be designed **based on** remaining **enzymatic activity**

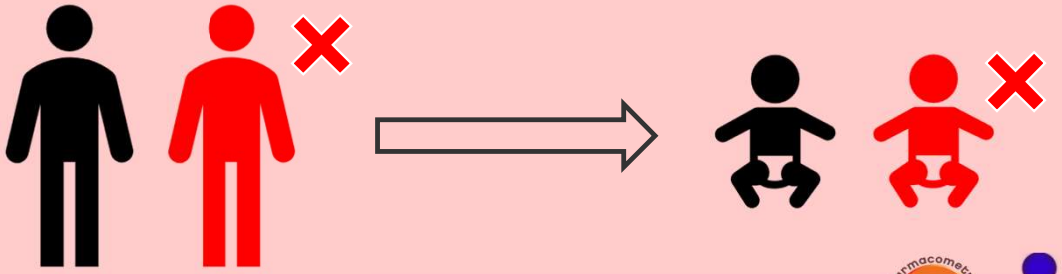
What´s next?

Validate patients' simulations using real world patient data



Develop optimal dosing tool (Amount and time of dosing)

Scale quantitative framework from adults to children



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