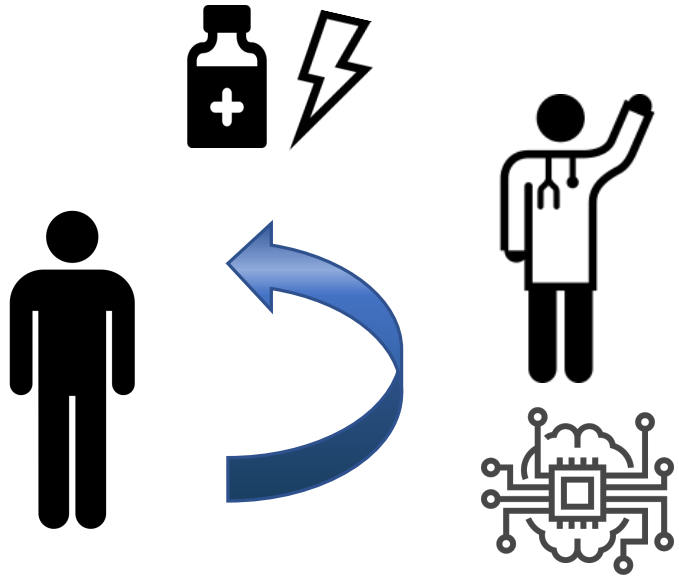
Personalized medicine (Neuromodulation technology) has individually tuned dose.

Based on:

1. Clinical endpoints
2. Biomarkers (three distinct kinds)
3. Triggers
4. Inclusion criteria



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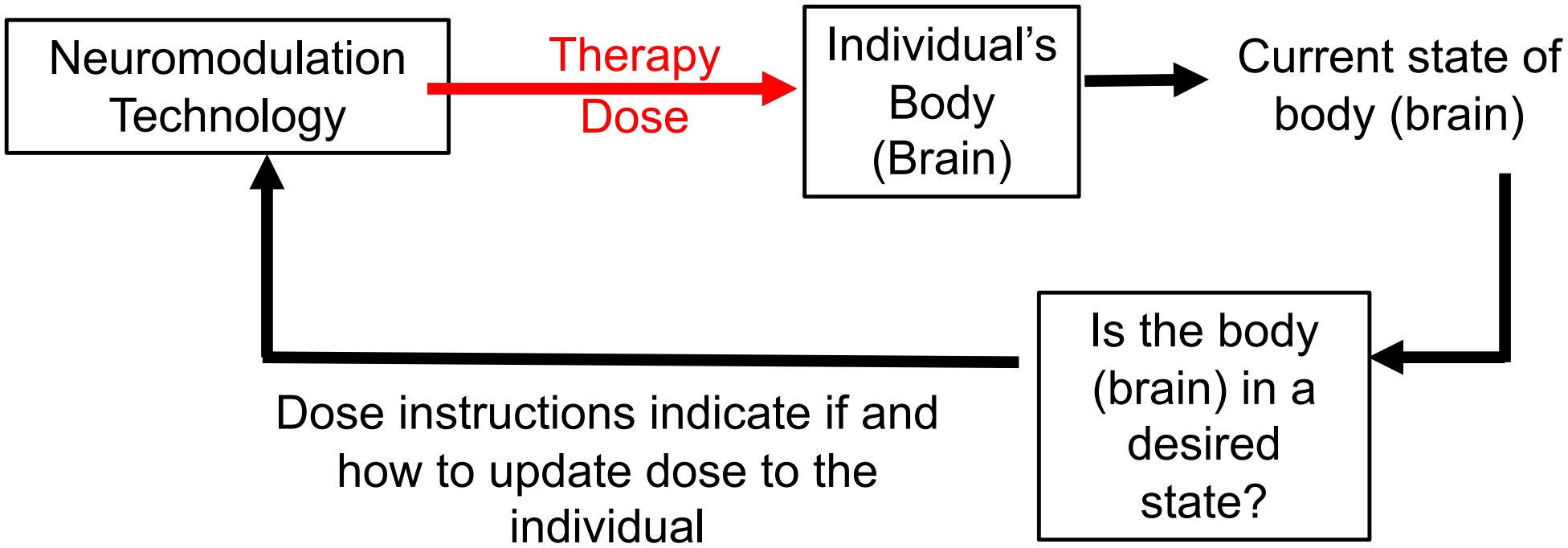

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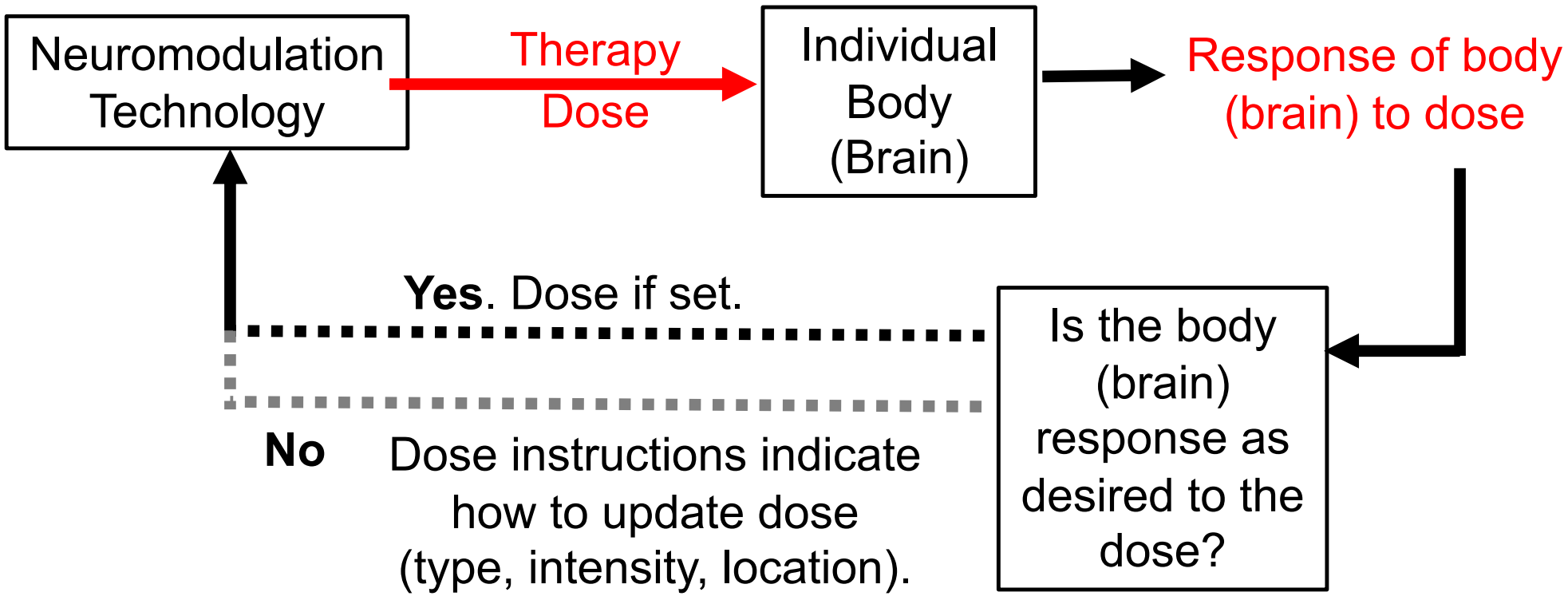

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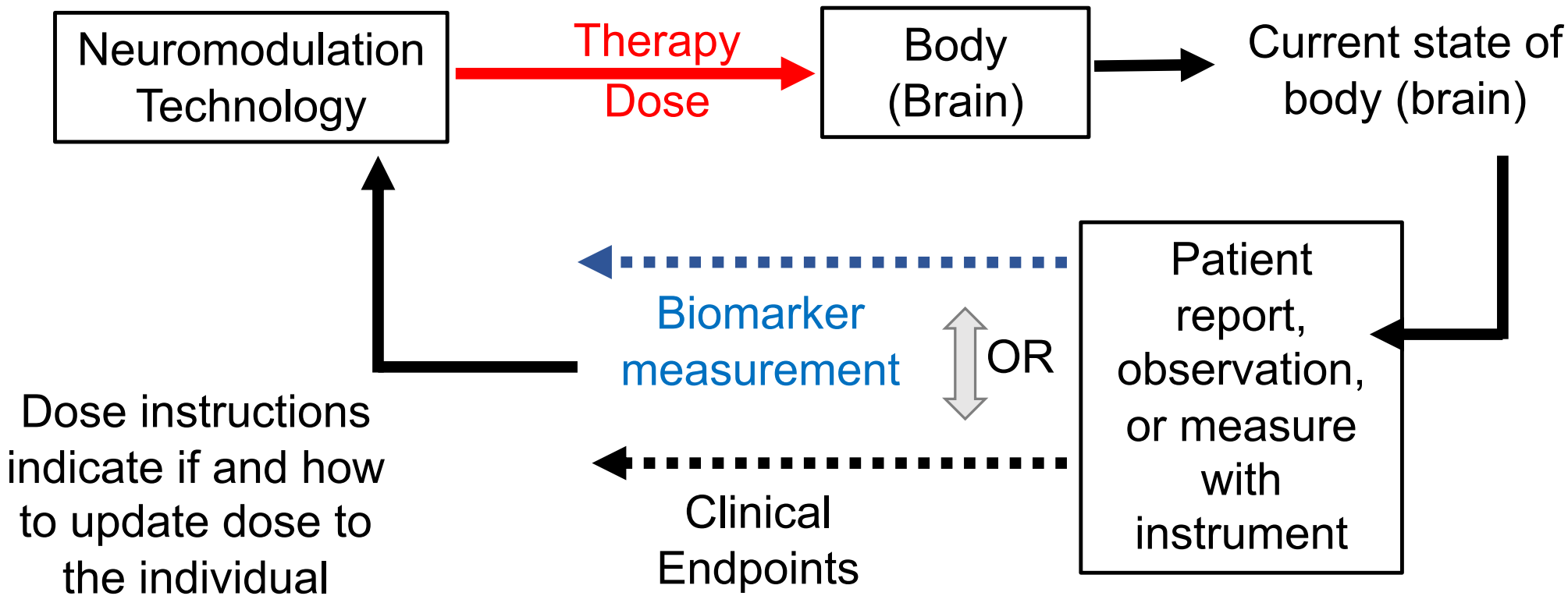


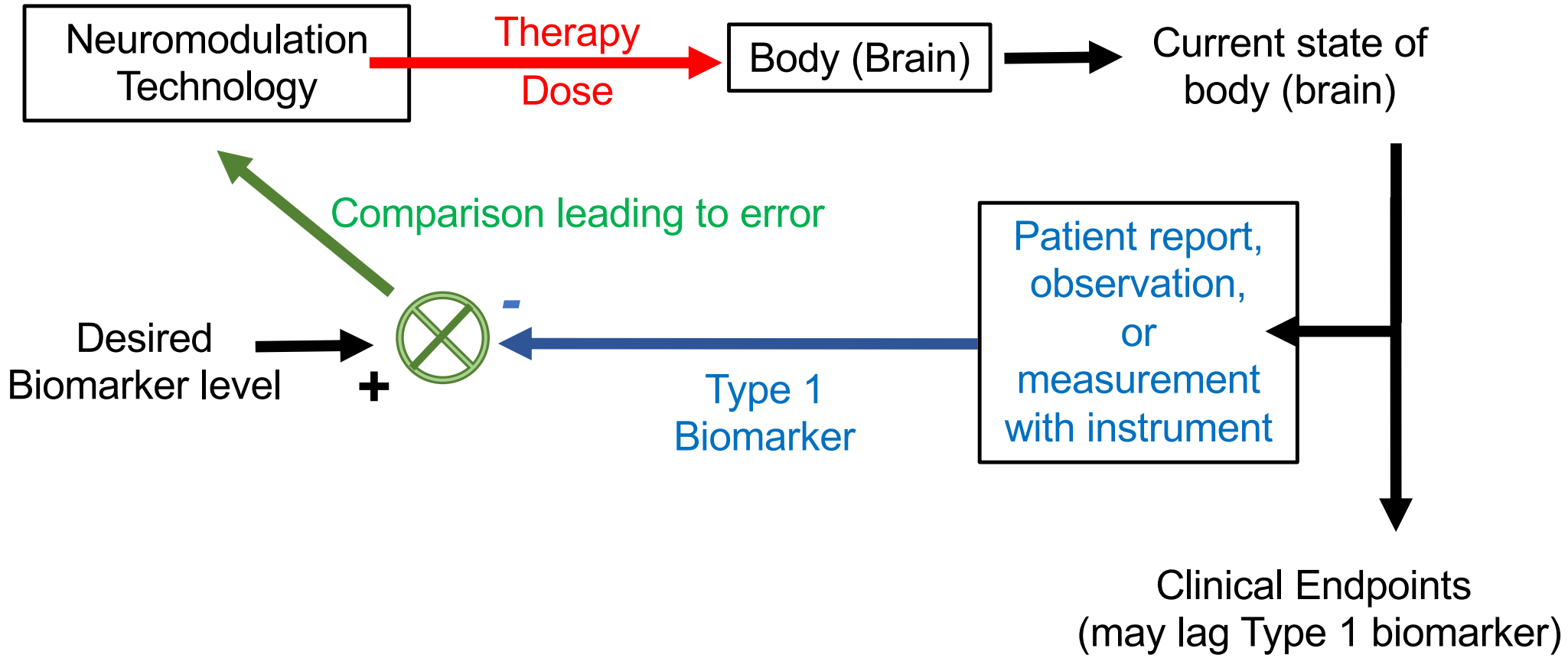
Personalized medicine (Neuromodulation technology) has individually tuned dose.

1. Clinical endpoints are the health outcomes underlying the indications for use. They respond to the intervention.
2. Biomarkers are subjective or objectives measures that respond to the intervention but are not clinical endpoints.

    A. Biomarker Type I. Tracks the clinical endpoint, but is not the clinical endpoint. Ideally *anticipates* changes in the clinical endpoint.

Using Biomarker Type 1 in Personalized Medicine

What measure to use, how to determine error, how to update dose based on error.



Personalized medicine (Neuromodulation technology) has individually tuned dose.

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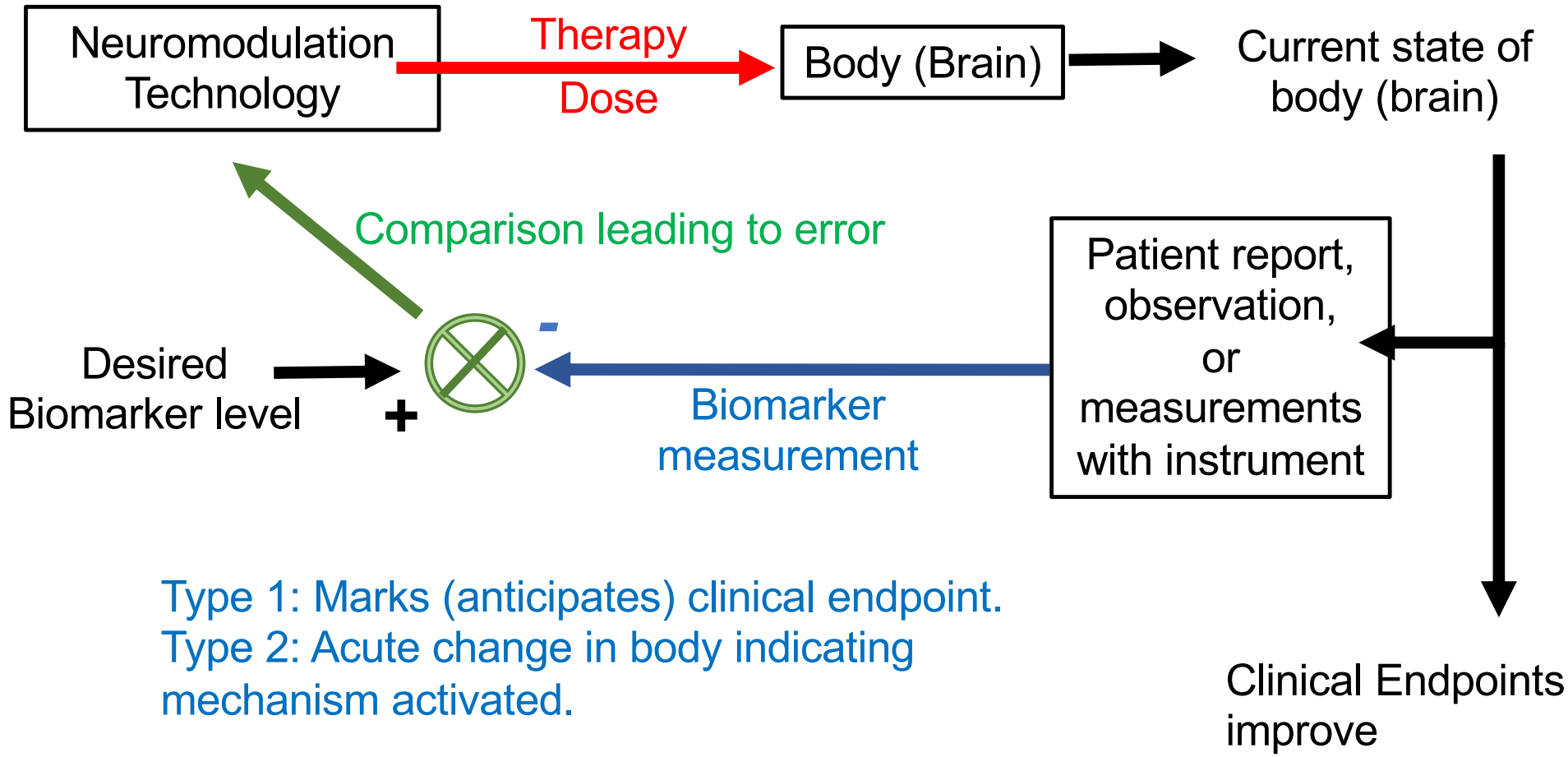
    A. Biomarker Type I. Tracks the clinical endpoint, but is not the clinical endpoint. Ideally anticipates changes in the clinical endpoint.

    B. Biomarker Type 2. Represents *acute* response to dose, and is not a biomarker of Type 1. Can be the mechanisms of action.

    Example: Tingling during some forms of pain neuromodulation.
    (Tingling masks the pain by “Gate Control” mechanism)

Using Biomarker Type 1 or Type 2 in Personalized Medicine



Type 1: Marks (anticipates) clinical endpoint.
Type 2: Acute change in body indicating mechanism activated.

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1. Clinical endpoints are the health outcomes underlying the indications for use. They respond to the intervention.
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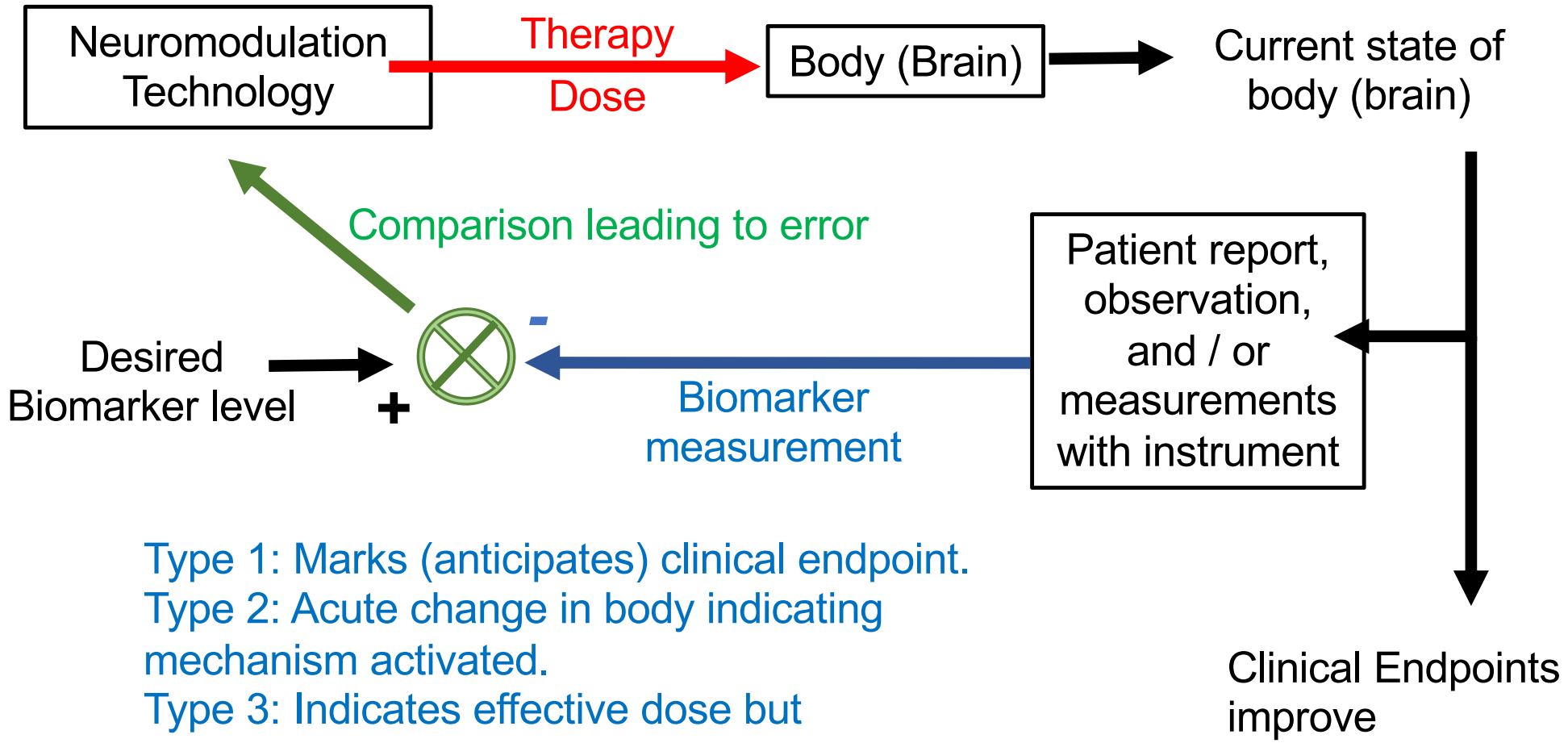
    A. Biomarker Type I. Tracks the clinical endpoint, but is not the clinical endpoint. Ideally anticipates changes in the clinical endpoint.

    B. Biomarker Type 2. Represents *acute* response to dose, and is not a biomarker of Type 1. Can be the mechanisms of action.

    C. Biomarker Type 3. Represents appropriate selection of dose, and is not a biomarker of Type 1 or Type 2.

Example: Finger twitch in TMS for depression.

Using Biomarker Type 1 or Type 2 or Type 3 in Personalized Medicine



Type 1: Marks (anticipates) clinical endpoint.
Type 2: Acute change in body indicating mechanism activated.
Type 3: Indicates effective dose but coincidental to mechanism / clinical endpoint.

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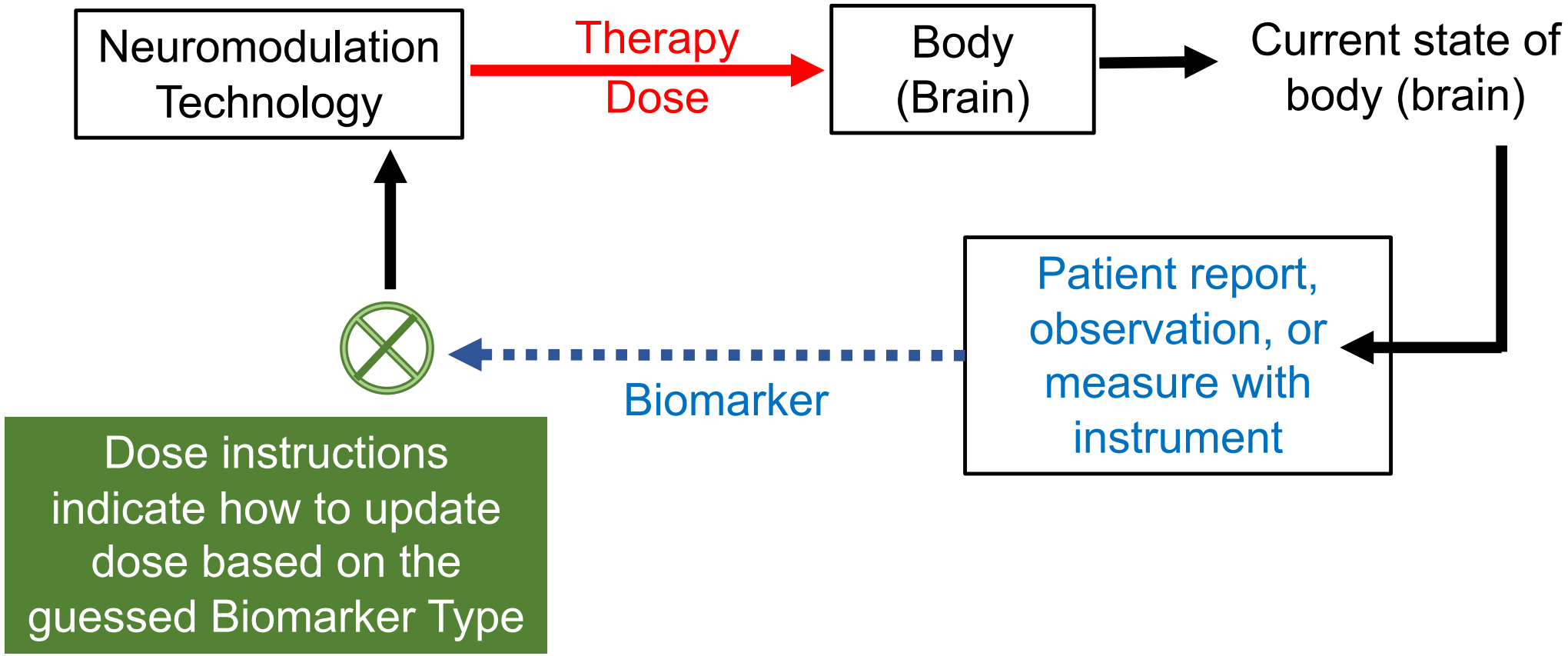
If the optimization method (loop) is the same for all three types of Biomarkers, does it matter to distinguish them?

Personalized medicine (Neuromodulation technology) has individually tuned dose.



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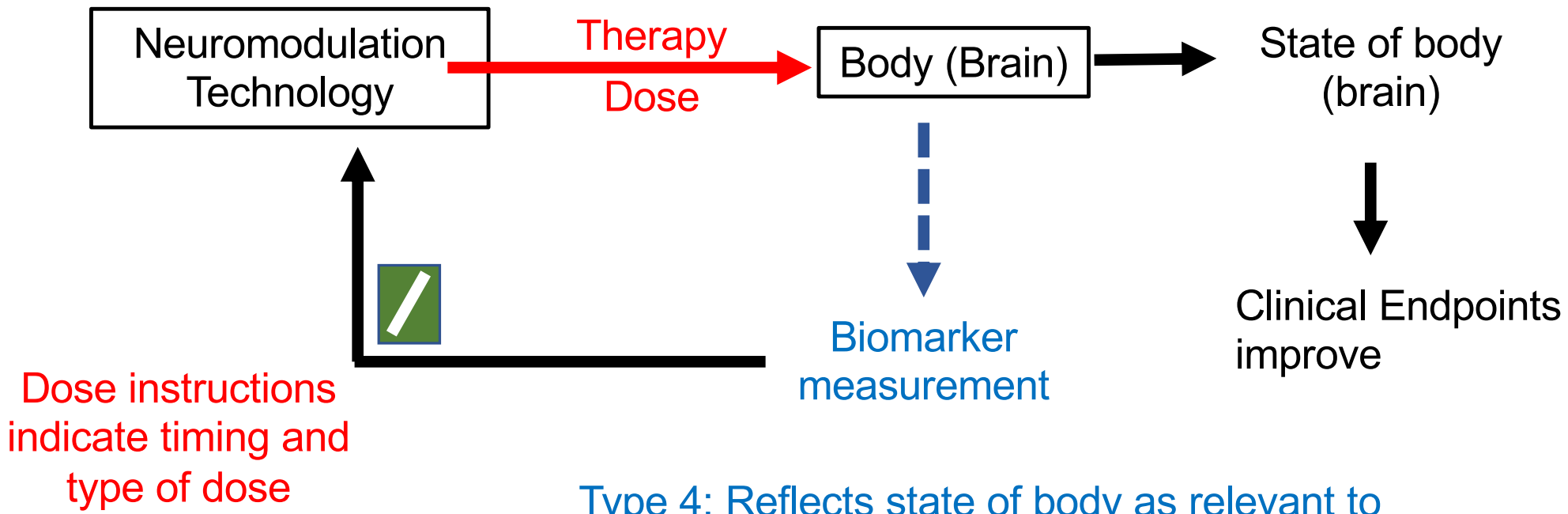
3. Triggers, are subject or objective measures that do *not* respond to the intervention and are used to tune dose.

Example: Heart rate of breathing gated stimulation (when not responsive to stimulation)

Using Biomarker Type 4 in Personalized Medicine



Type 4: Reflects state of body as relevant to effects of dose, but does not respond to dose

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    A. Biomarker Type I. Tracks the clinical endpoint, but is not the clinical endpoint. Ideally anticipates changes in the clinical endpoint.

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    C. Biomarker Type 3. Represents appropriate selection of dose, and is not a biomarker of Type 1 or Type 2.

3. Triggers, are subject or objective measures that do not respond to the intervention and are used to tune dose.

4. Inclusion criteria. Govern subject selection for varied purposed (eg. trial success)