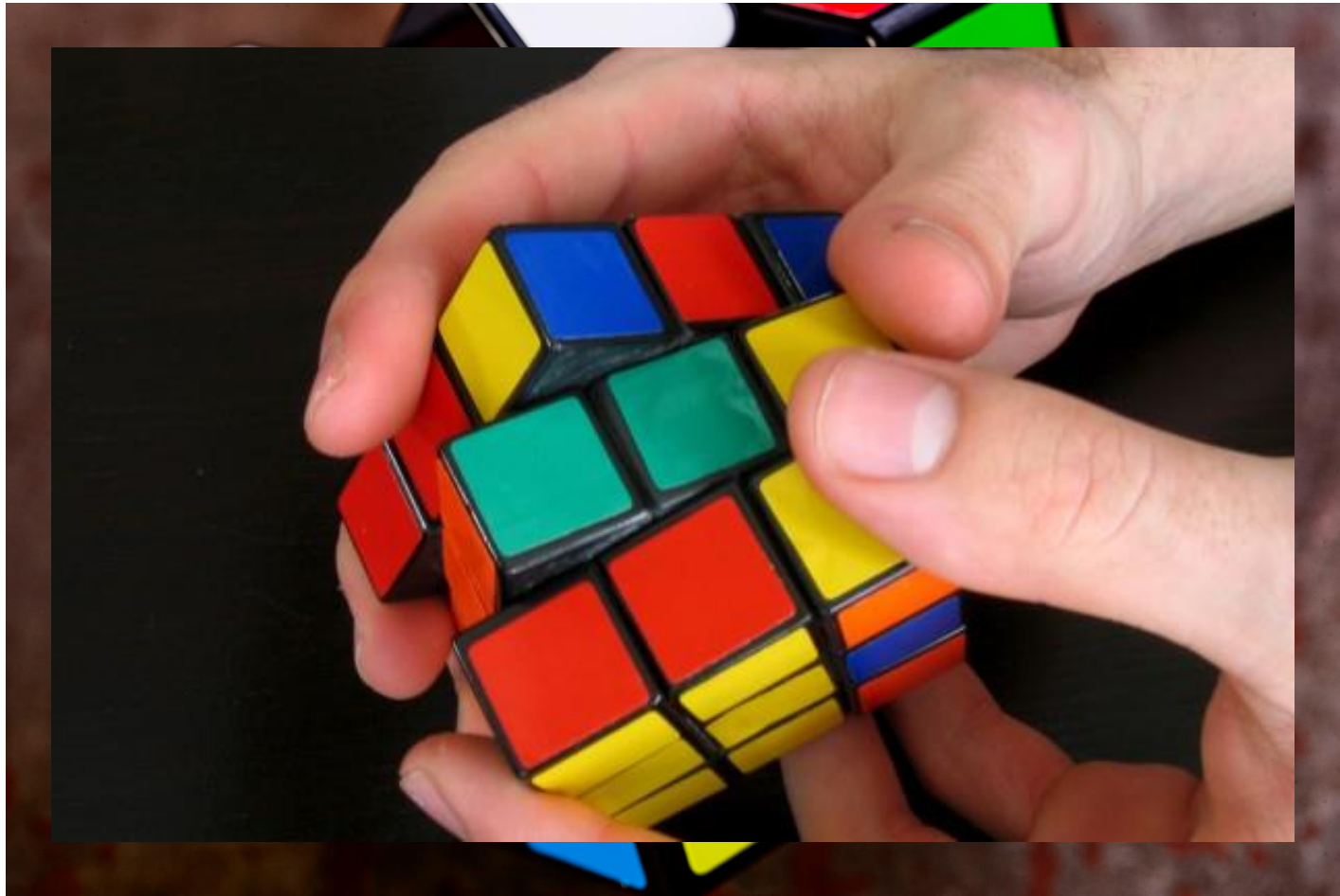


MANAGEMENT STRATEGIES IN MULTIPLE SCLEROSIS

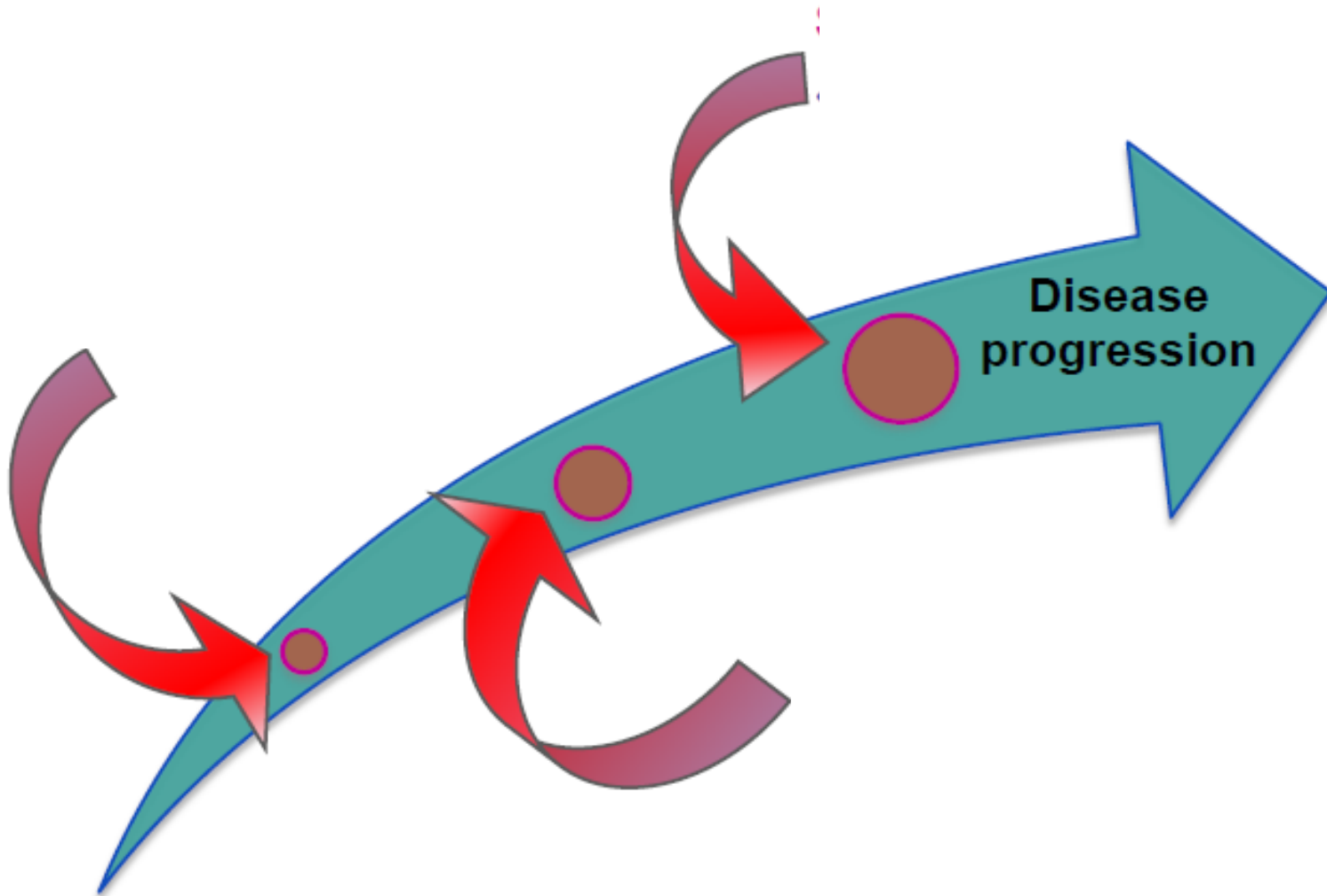
Amr Hassan MD,FEBN
Associate professor of Neurology
Cairo University



Navigating the multiple facets of management of MS



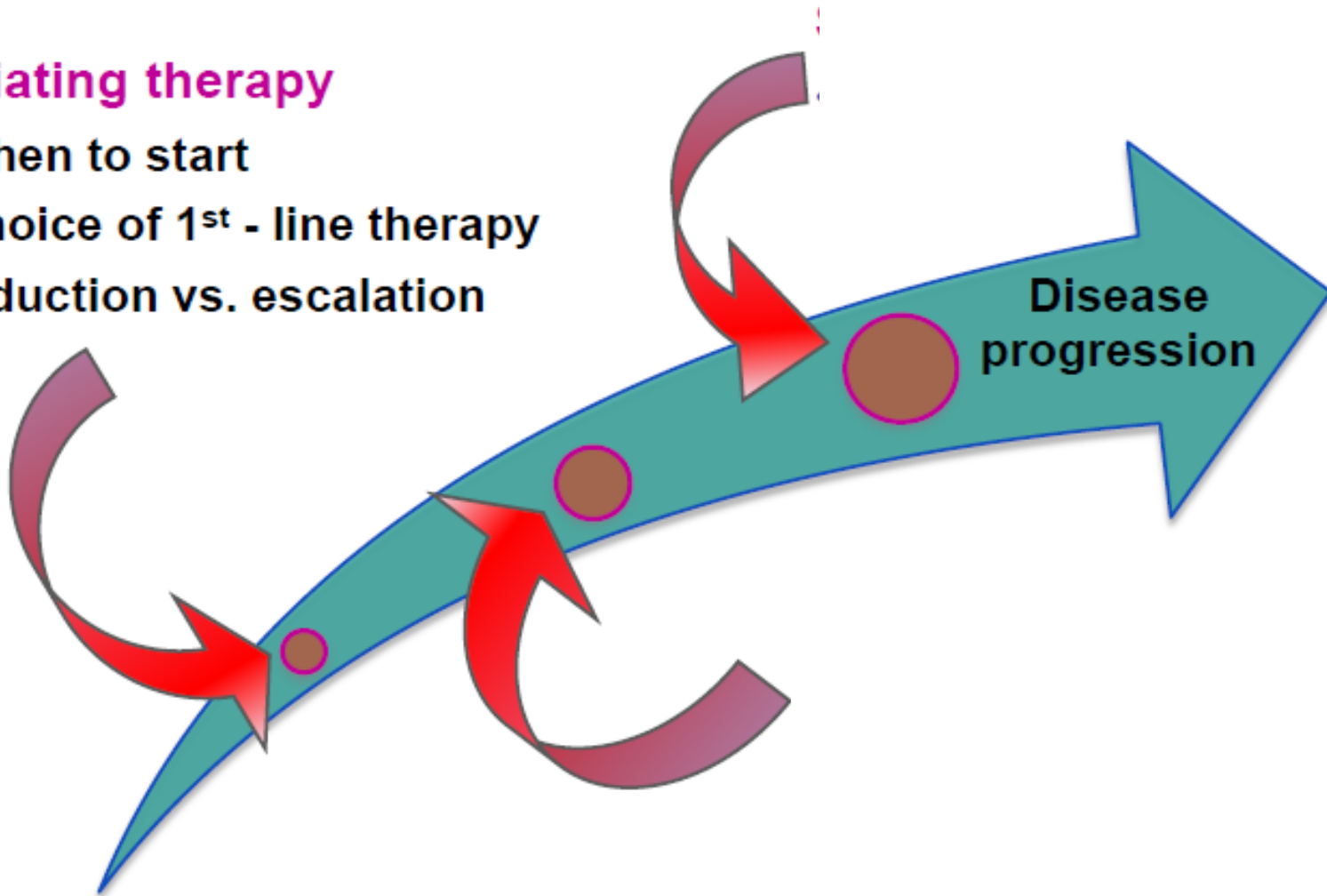
Key decision making points in Treatment of MS



Key decision making points in Treatment of MS

Initiating therapy

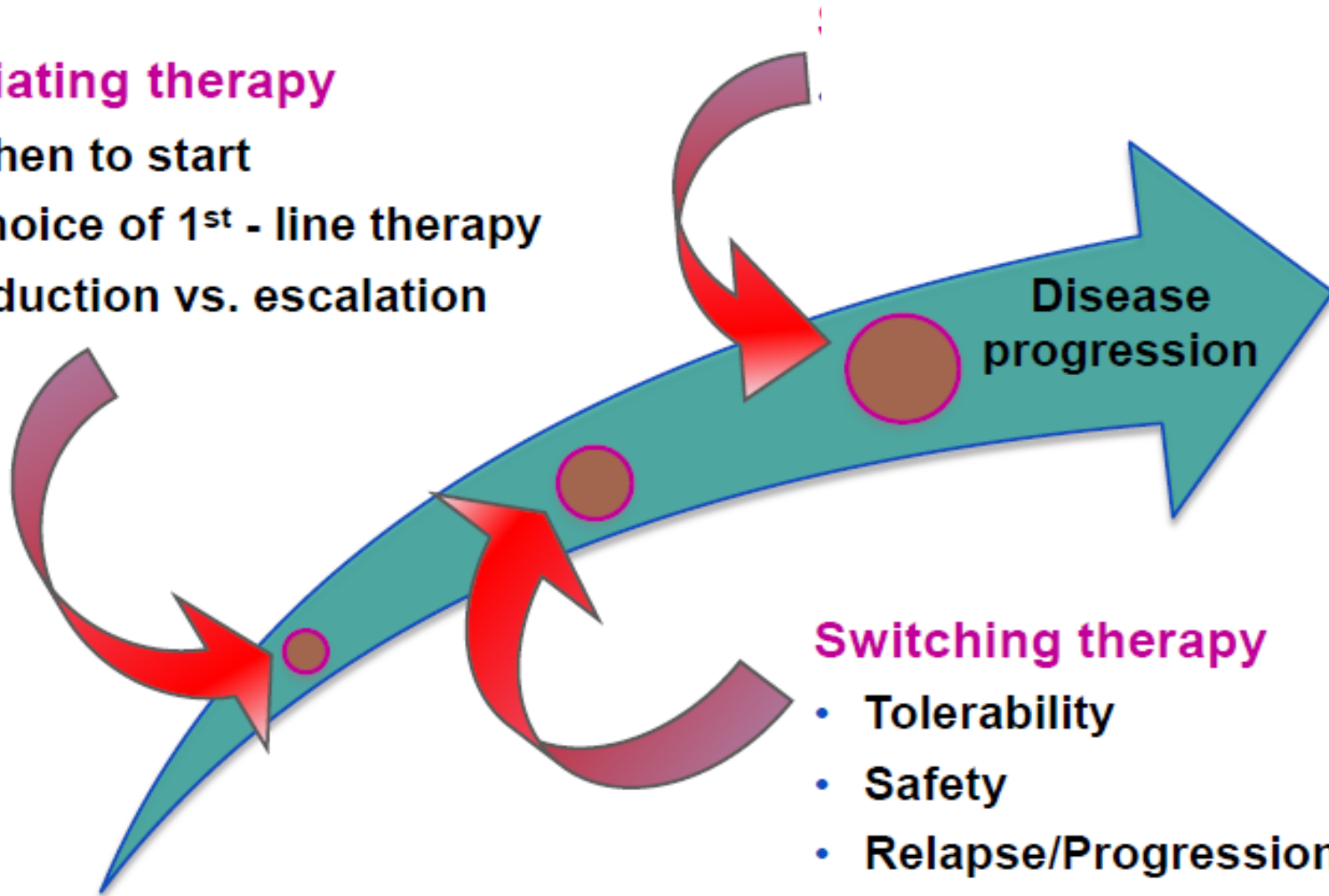
- When to start
- Choice of 1st - line therapy
- Induction vs. escalation



Key decision making points in Treatment of MS

Initiating therapy

- When to start
- Choice of 1st - line therapy
- Induction vs. escalation



Switching therapy

- Tolerability
- Safety
- Relapse/Progression/MRI

Key decision making points in Treatment of MS

Initiating therapy

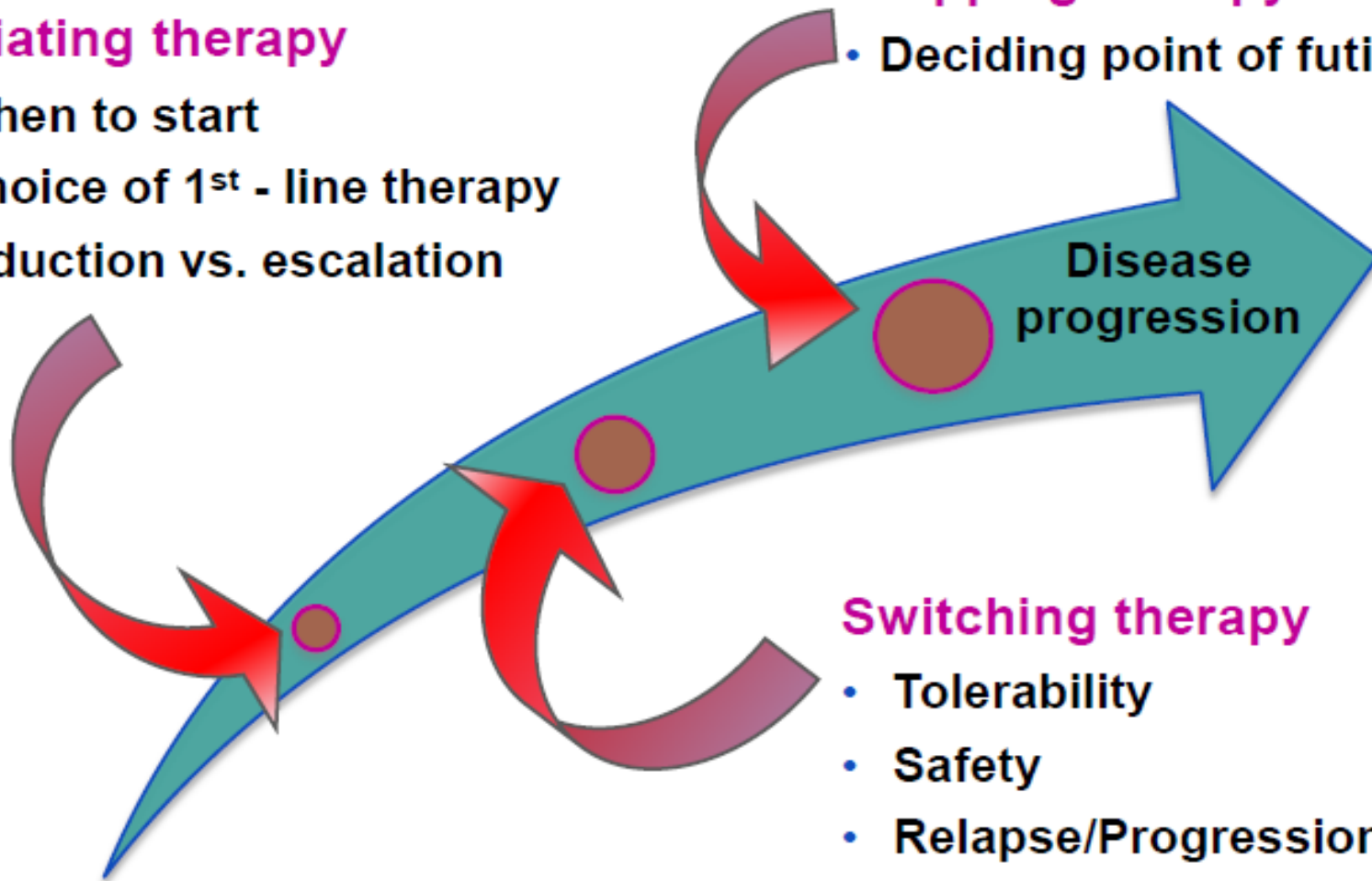
- When to start
- Choice of 1st - line therapy
- Induction vs. escalation

Stopping therapy

- Deciding point of futility

Switching therapy

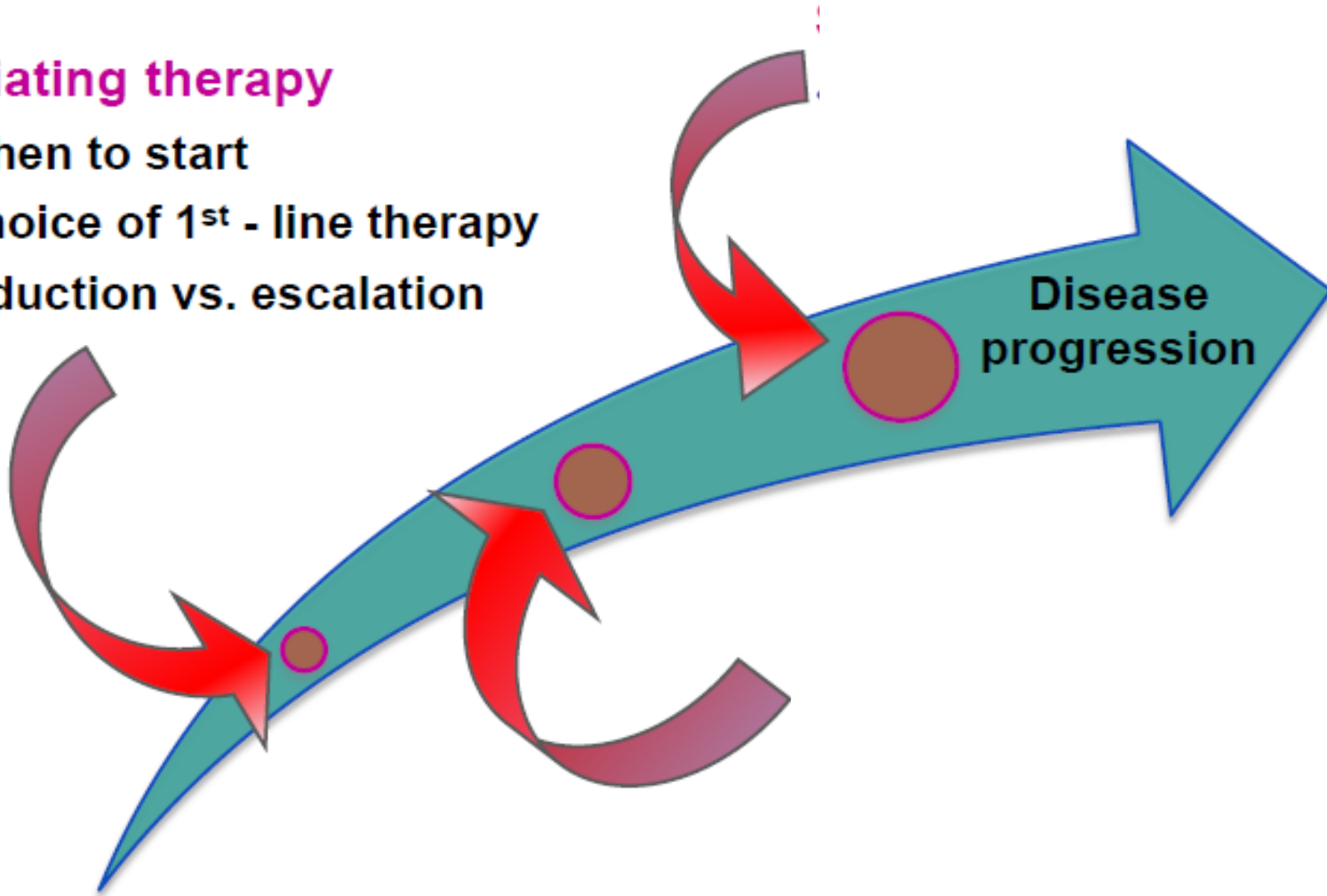
- Tolerability
- Safety
- Relapse/Progression/MRI

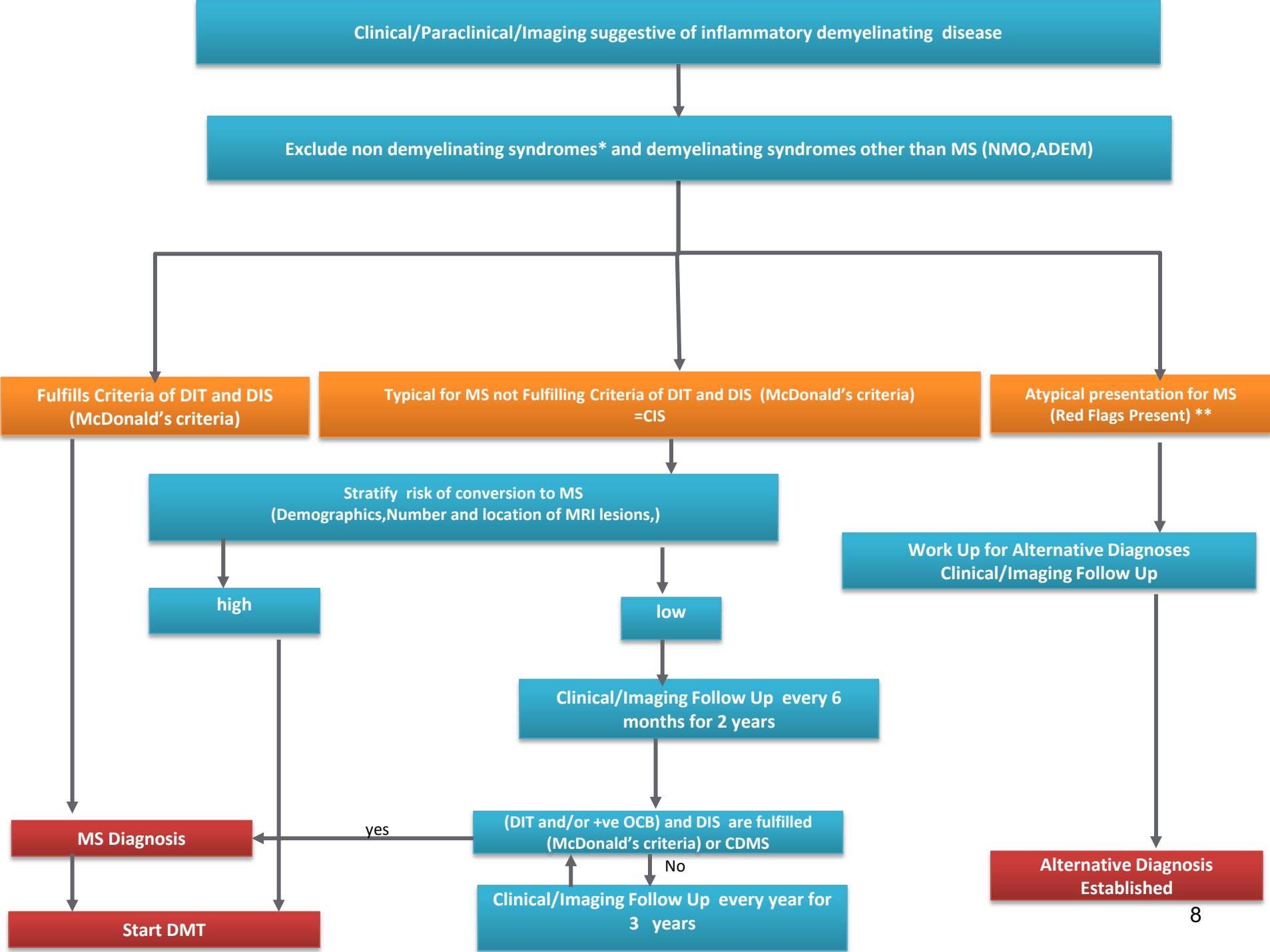


Key decision making points in Treatment of MS

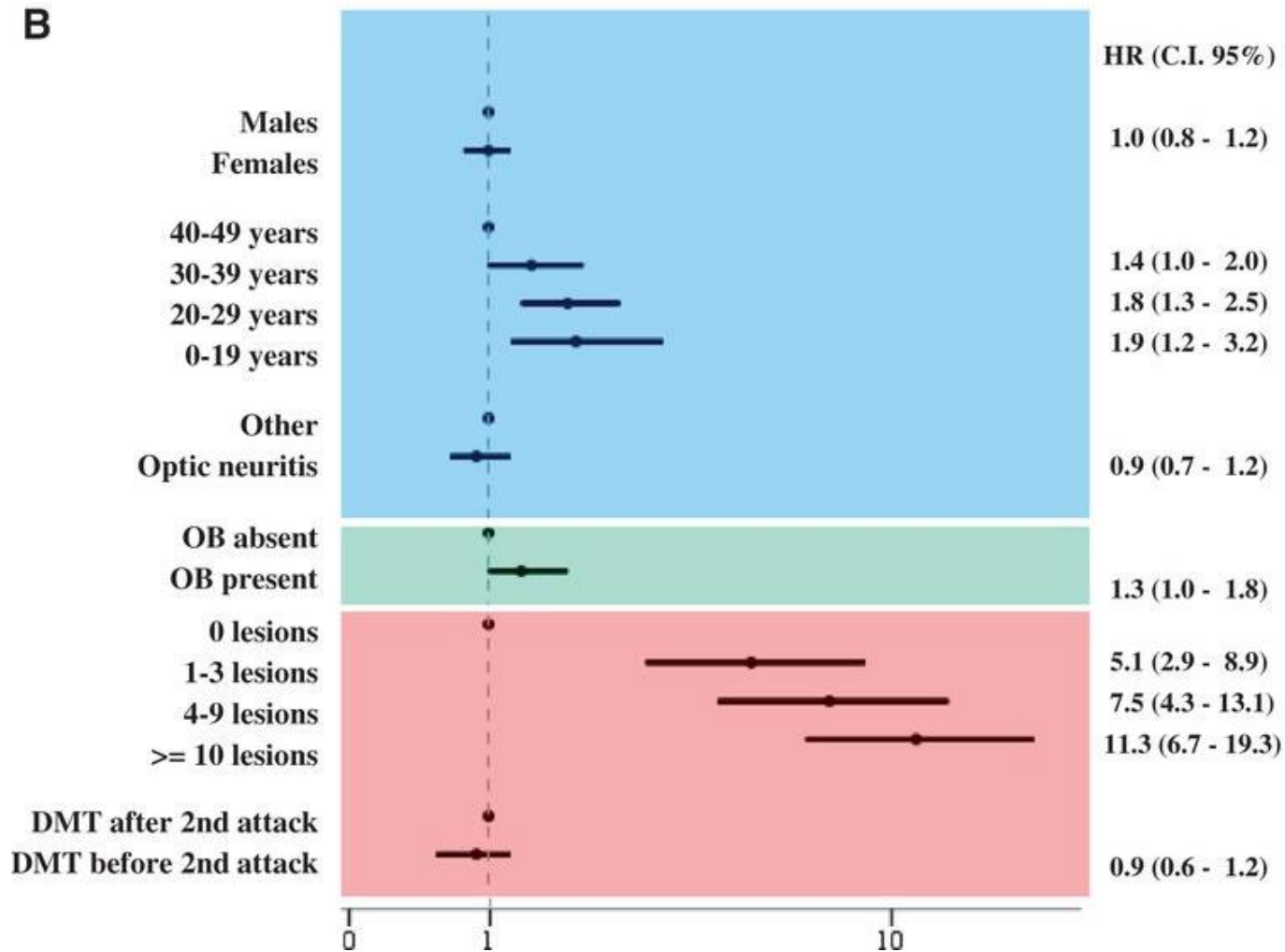
Initiating therapy

- When to start
- Choice of 1st - line therapy
- Induction vs. escalation



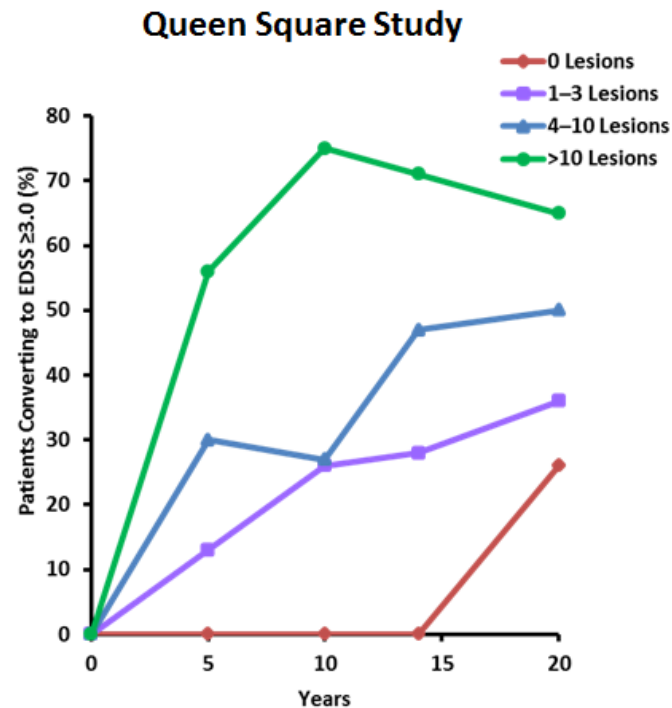


Effect of baseline clinical, biological and MRI characteristics on the conversion to CDMS



Effect of baseline clinical, biological and MRI characteristics on the conversion to CDMS

Baseline number of brain lesions predicts progression to EDSS Score ≥ 3.0



The data presented for years 5, 10, 14, and 20 were obtained from different publications based on the same longitudinal study.
The exact relationship between MRI findings and the clinical status of the patient is unknown.
Fisniku LK et al. *Brain*. 2008;131:808-817; Morrissey SP et al. *Brain*. 1993;116:135-146;
O'Riordan JI et al. *Brain*. 1998;121:495-503; Brex PA et al. *N Engl J Med*. 2002;346:158-164.

Practice guideline recommendations summary: Disease-modifying therapies for adults with multiple sclerosis

Report of the Guideline Development, Dissemination, and Implementation
Subcommittee of the American Academy of Neurology

Statement 7a

Clinicians should discuss the benefits and risks of DMTs for people with a single clinical demyelinating event with 2 or more brain lesions that have imaging characteristics consistent with MS (Level B).

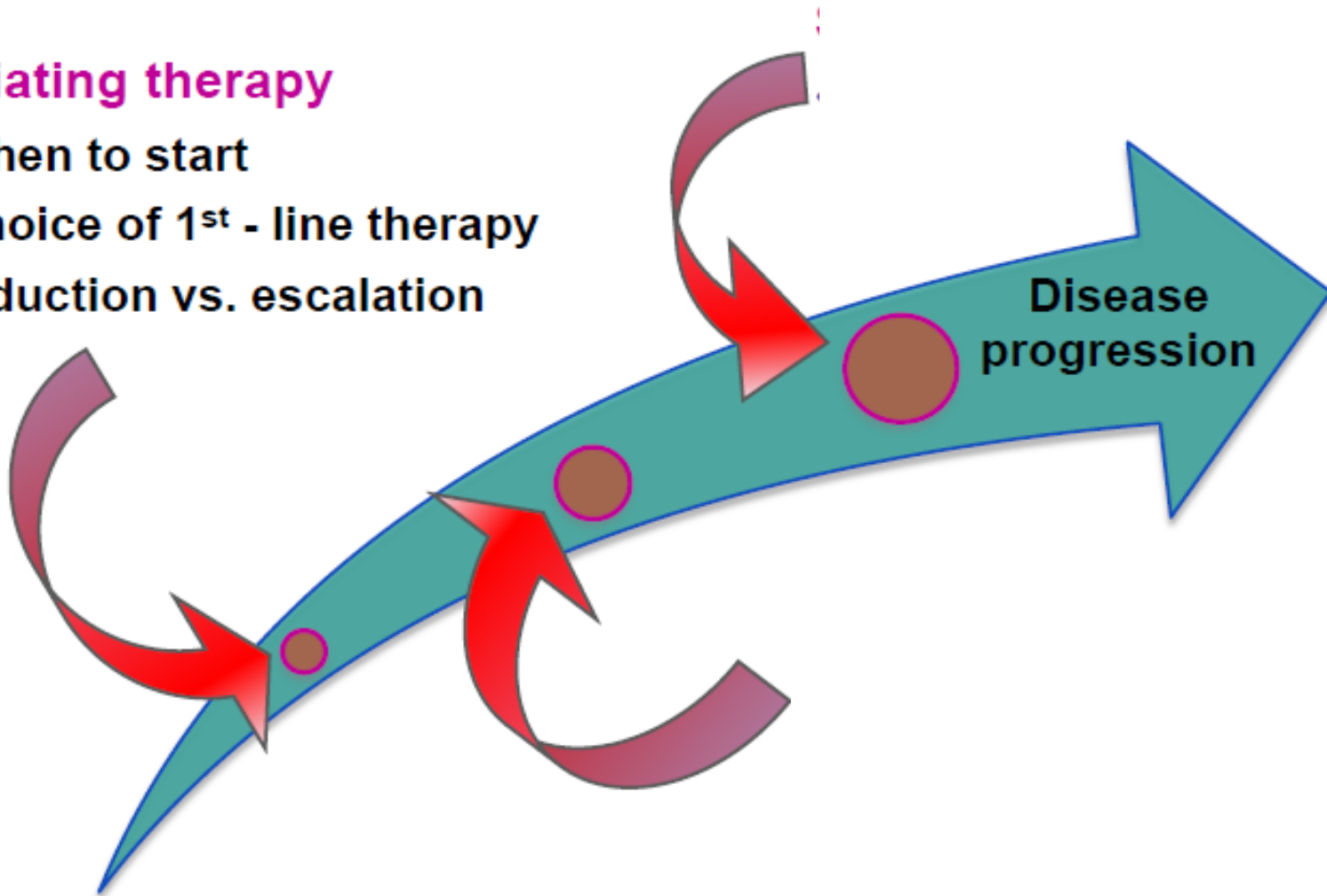
Statement 7b

After discussing the risks and benefits, clinicians should prescribe DMT to people with a single clinical demyelinating event and 2 or more brain lesions characteristic of MS who decide they want this therapy (Level B).

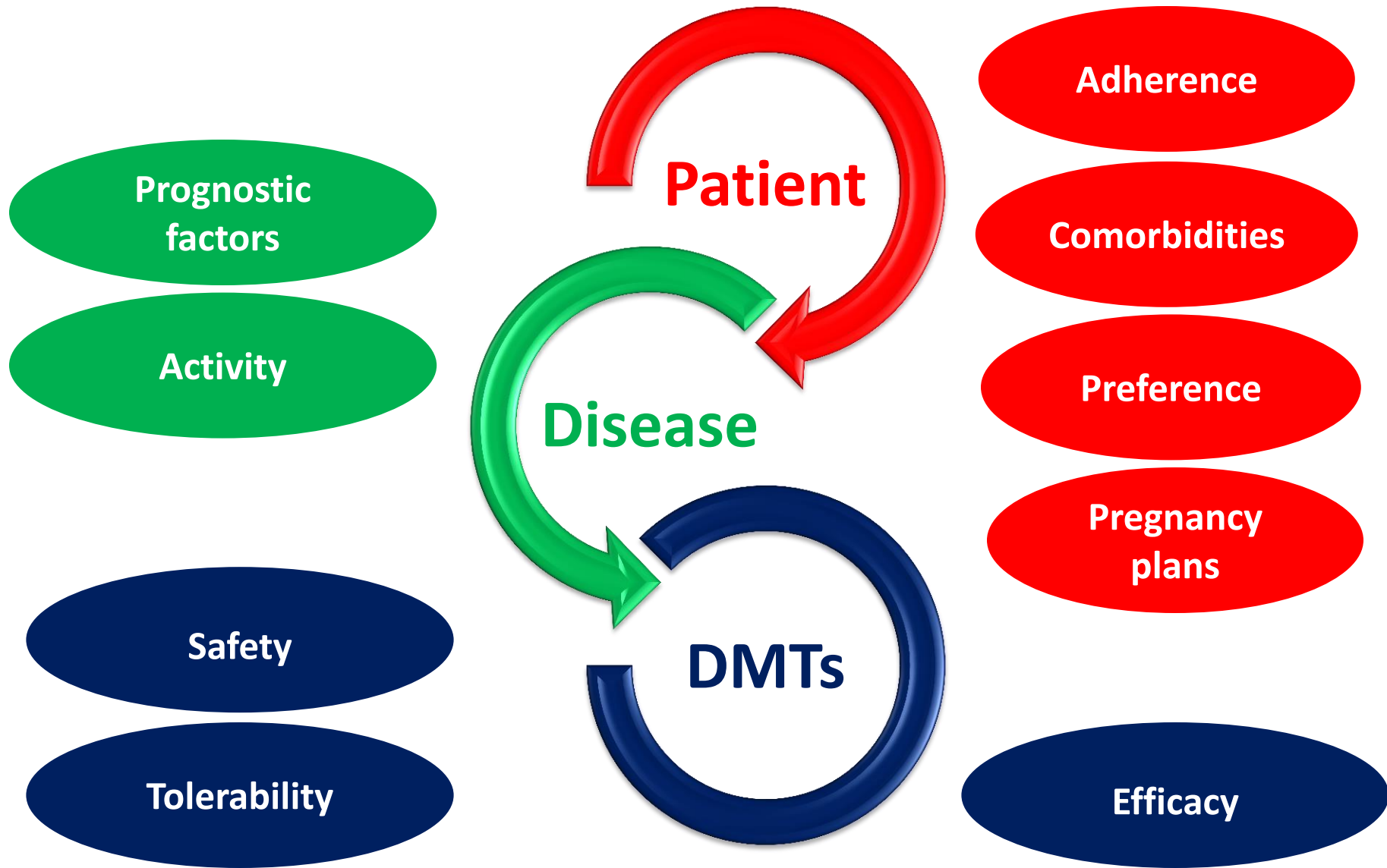
Key decision making points in Treatment of MS

Initiating therapy

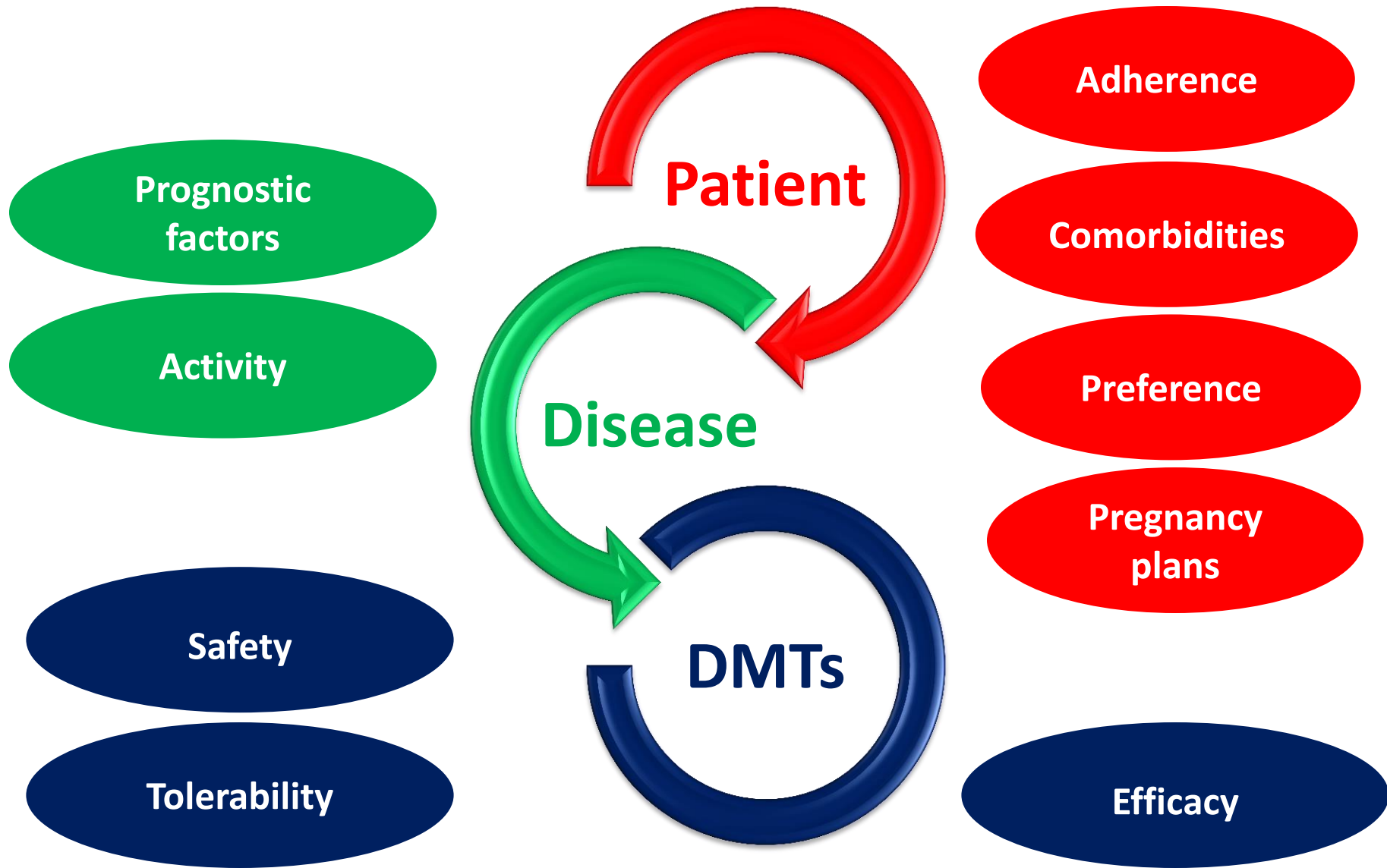
- When to start
- Choice of 1st - line therapy
- Induction vs. escalation



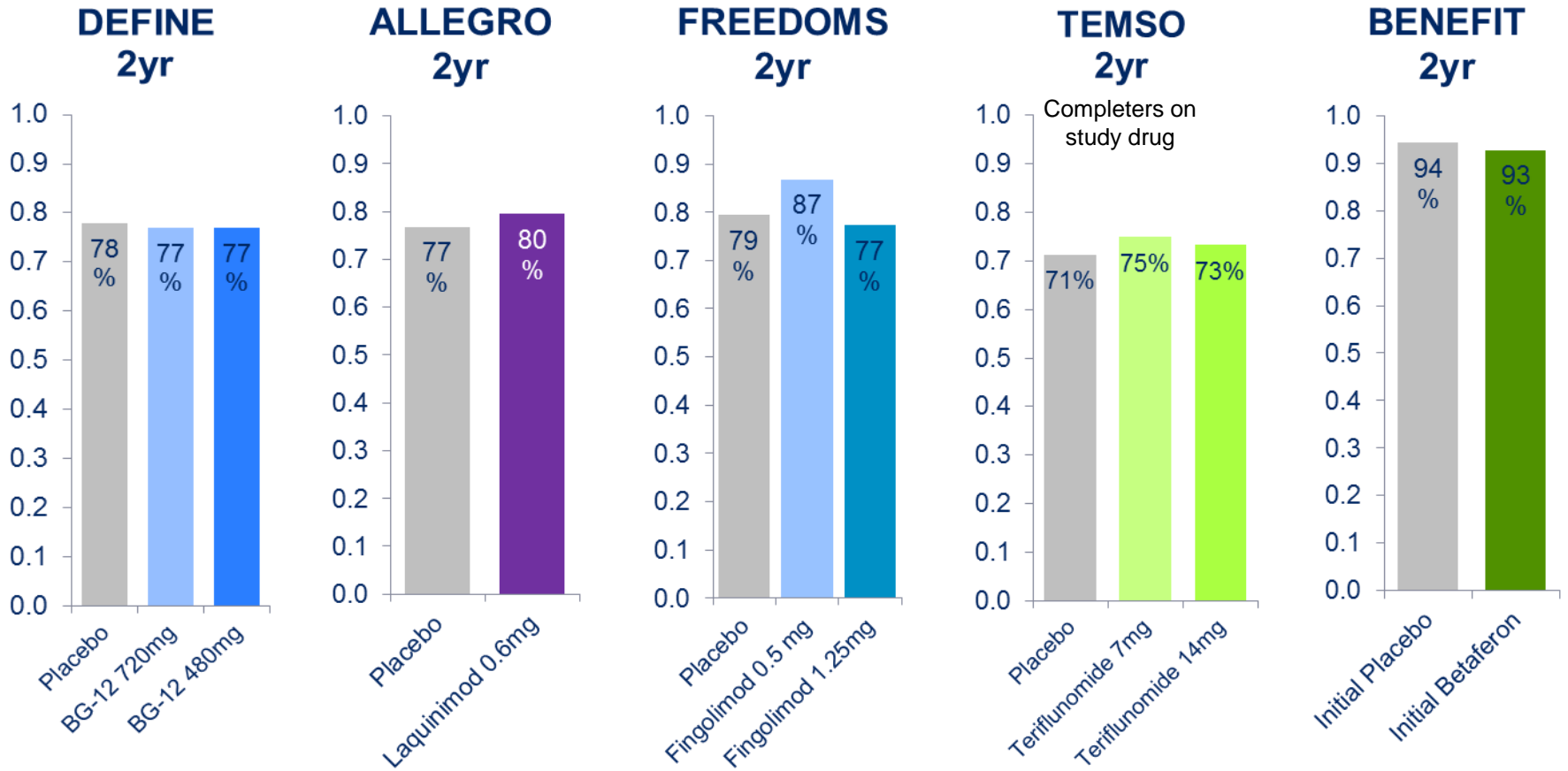
Factors governing Choice of the 1st line therapy



Factors governing Choice of the 1st line therapy

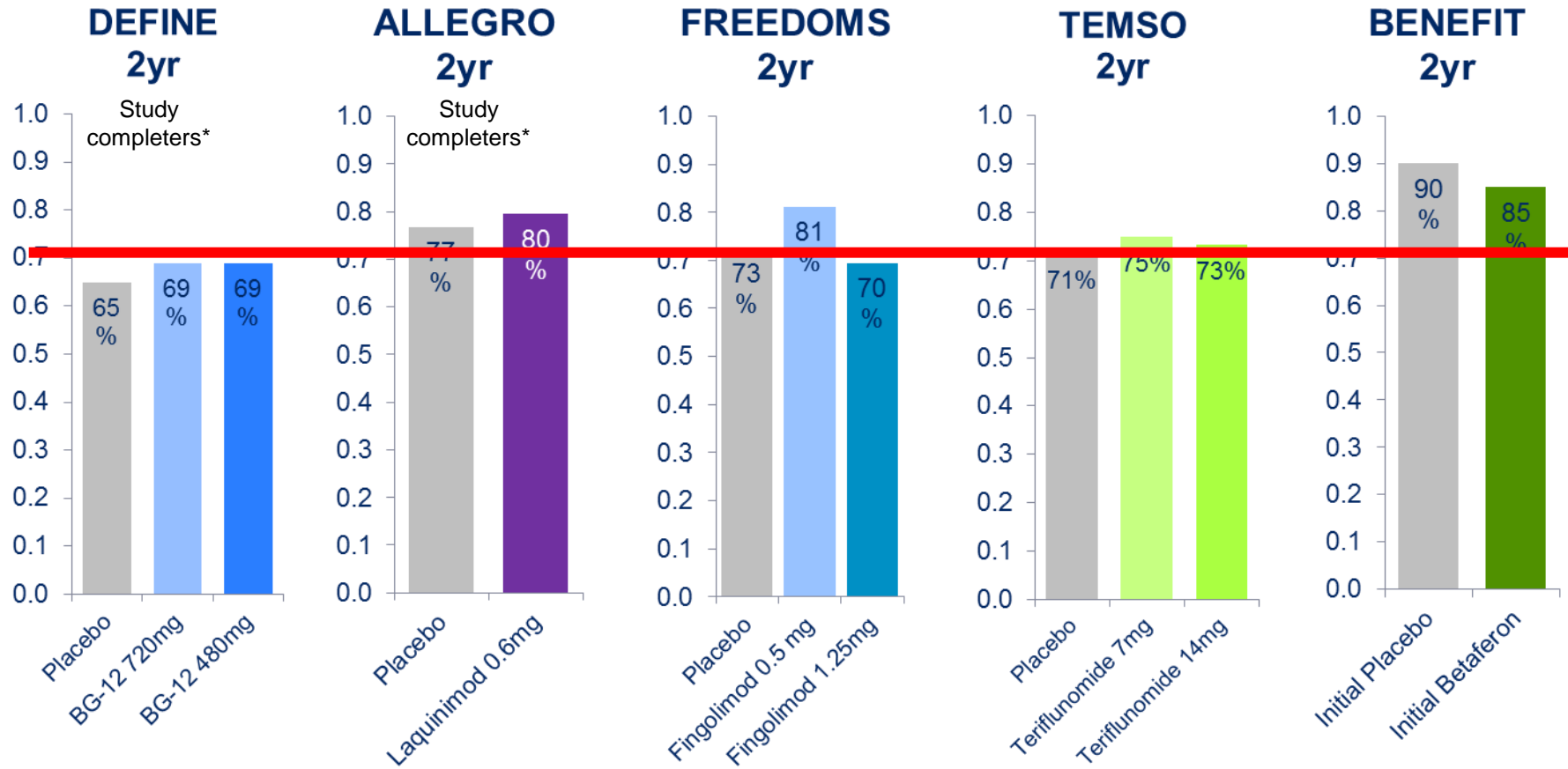


Study Completers in Recent Clinical Trials



Gold et al, NEJM 2012, Comi et al, NEJM 2012, Kappos et al, NEJM 2010, O'Connor et al, NEJM 2011, Kappos et al, Neurology 2006

Study Drug Adherence Rates in Recent Clinical Trials



*No information whether these patients are still taking the medication provided.

Gold et al, NEJM 2012, Comi et al, NEJM 2012, Kappos et al, NEJM 2010, O'Connor et al, NEJM 2011, Kappos et al, Neurology 2006

Reason for Nonadherence

- Perceived inefficacy and patient's expectation (treatment didn't improve how they feel).
- Patient satisfaction with the medication.
- Lack of knowledge of the value of being adherent.
- Side effects (specially injection site reactions).
- Forgetfulness.
- Character, age.
- Depression.
- Quality of the patient/physician relationship.

Improving patient adherence

Route of administration



Low monitoring requirements



Durable efficacy /Well tolerated treatment



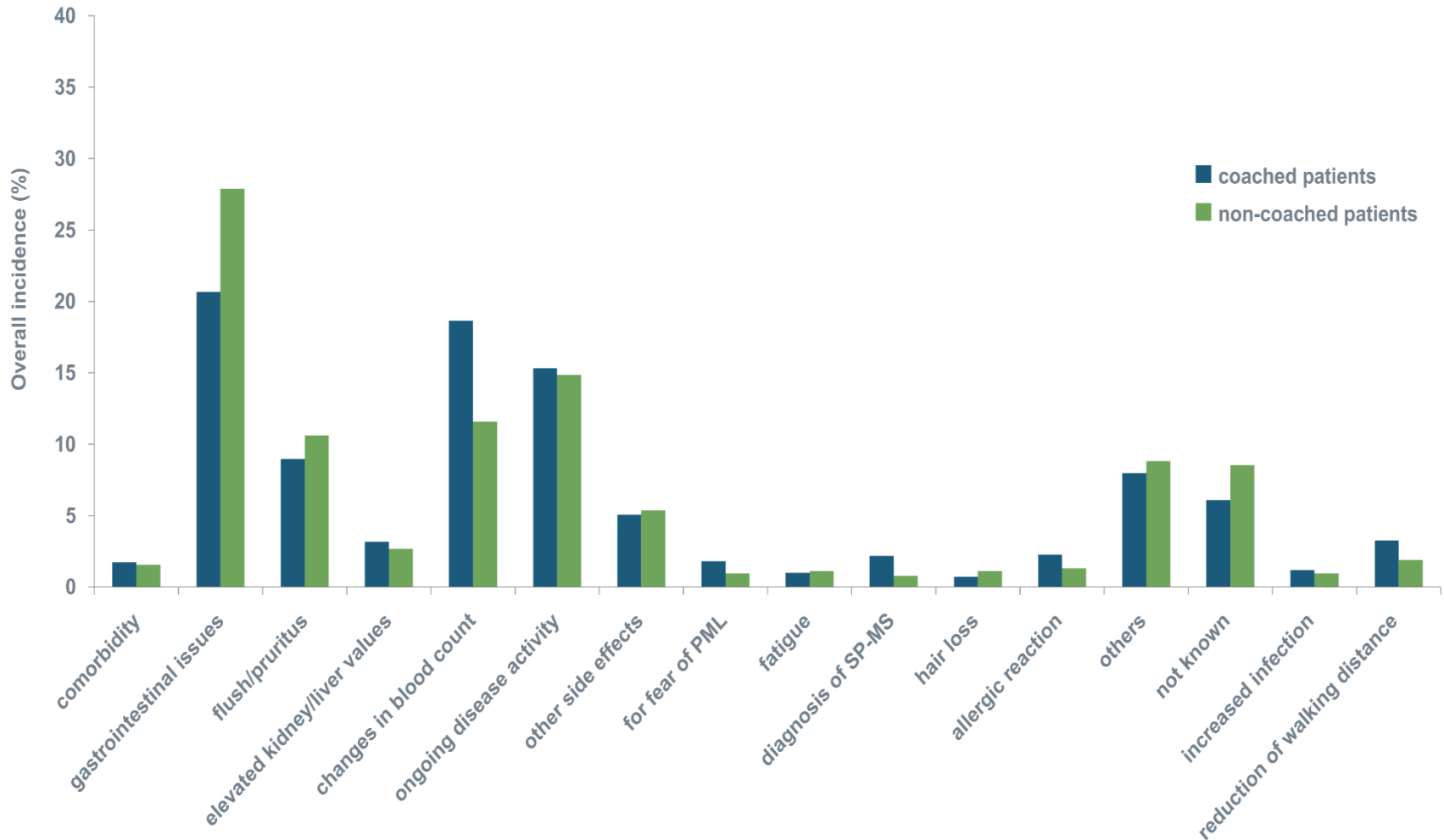
Practice guideline recommendations summary: Disease-modifying therapies for adults with multiple sclerosis

Report of the Guideline Development, Dissemination, and Implementation
Subcommittee of the American Academy of Neurology

Statement 3

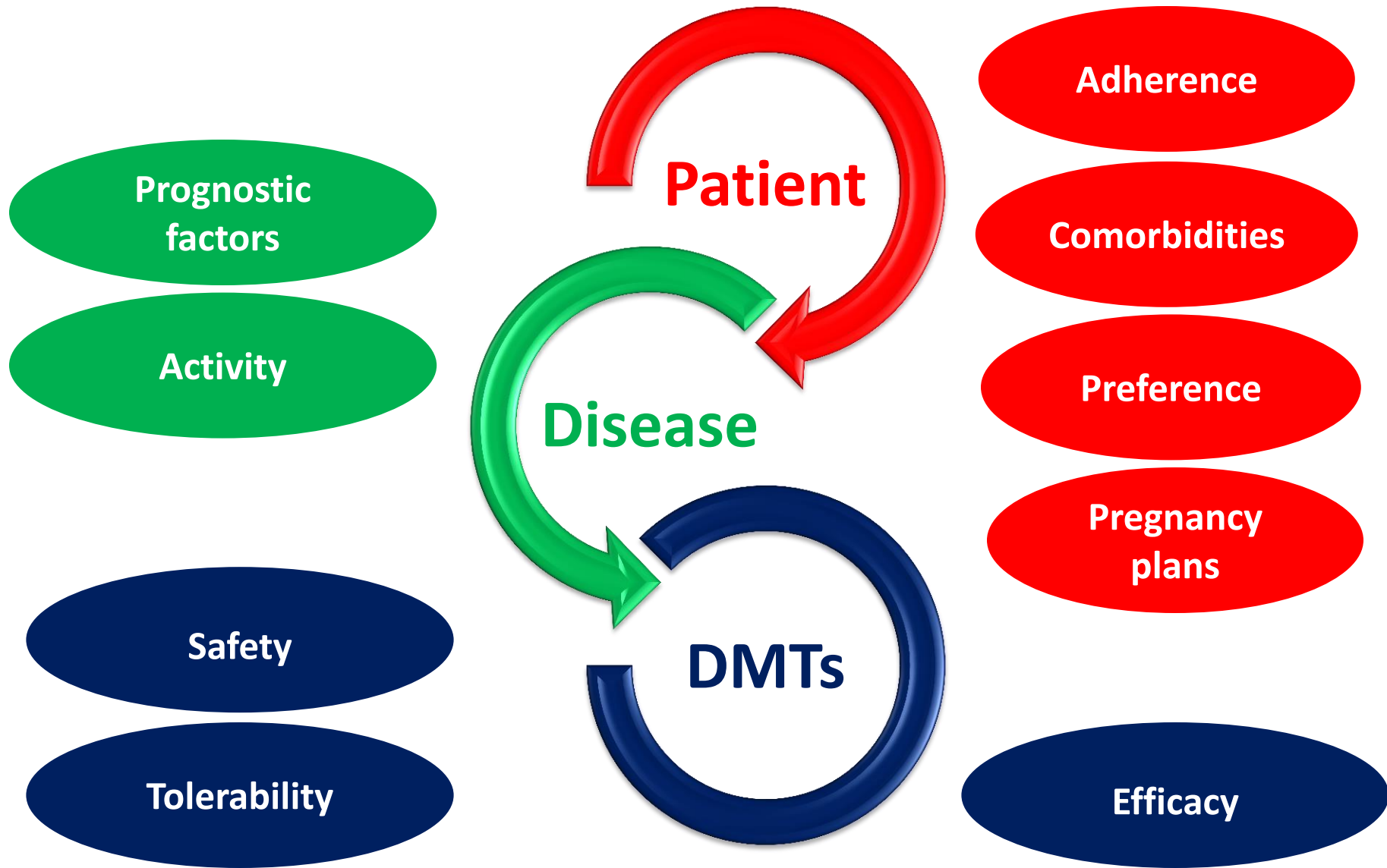
Clinicians should discuss a change to noninjectable or less frequently injectable DMTs in people with MS who report intolerable discomfort with the injections or in those who report injection fatigue on injectable DMTs (Level B).

Individualized Patient Coaching: Reasons for Therapy Discontinuation and Dropout

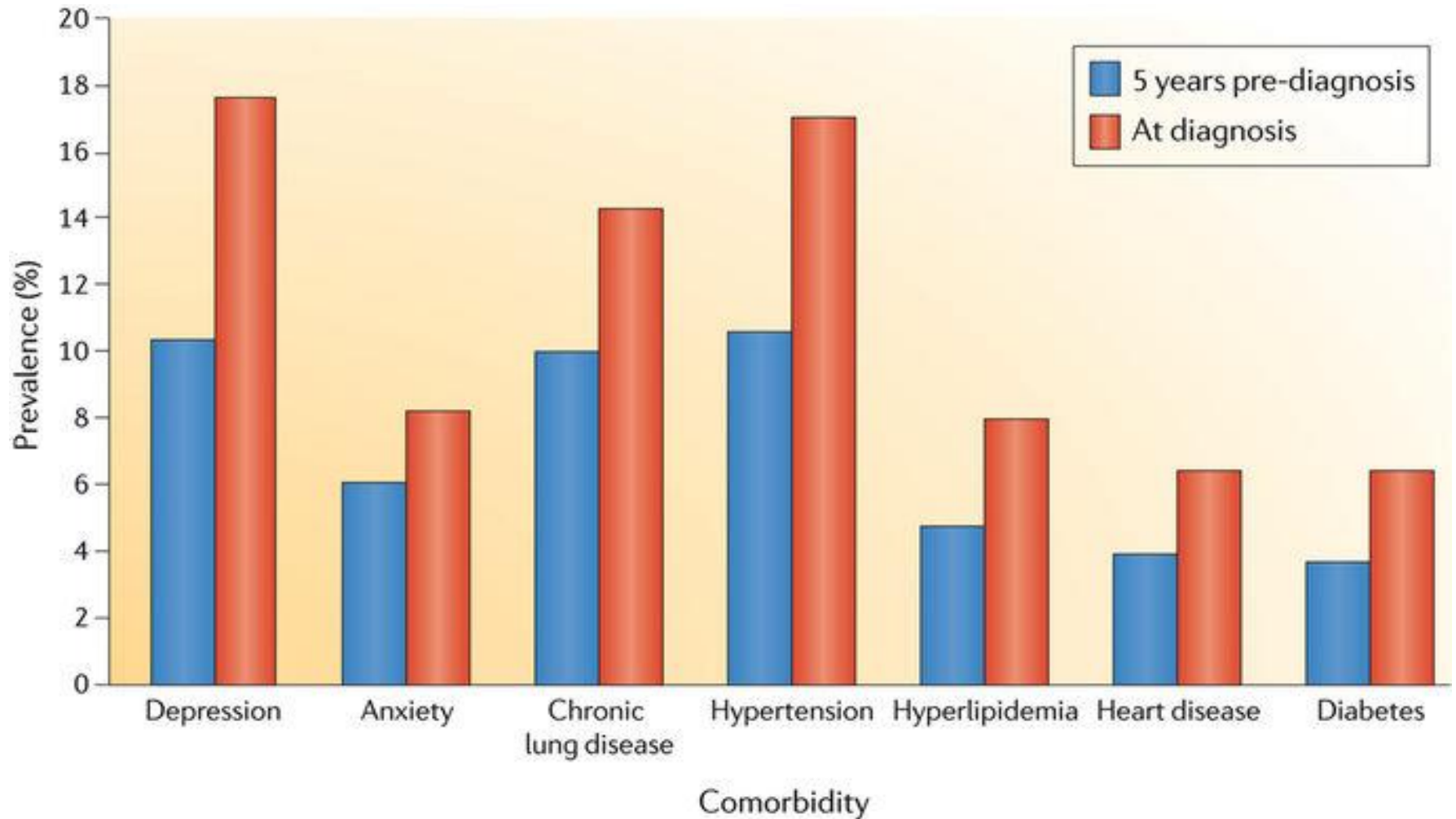


Begus-Nahrman Y et al. Presented at ECTRIMS; September 14–17, 2016; London, UK, P1214.

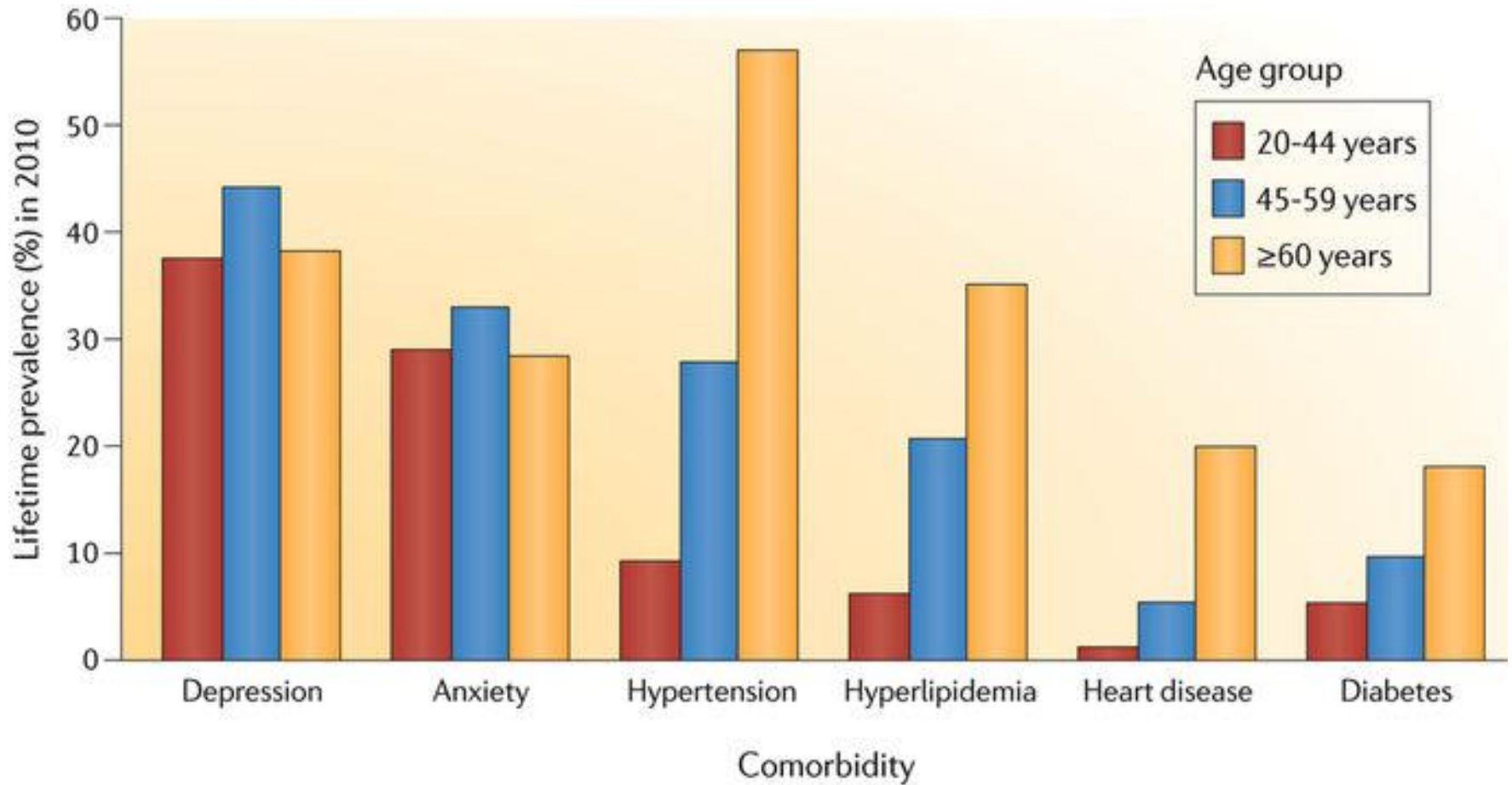
Factors governing Choice of the 1st line therapy



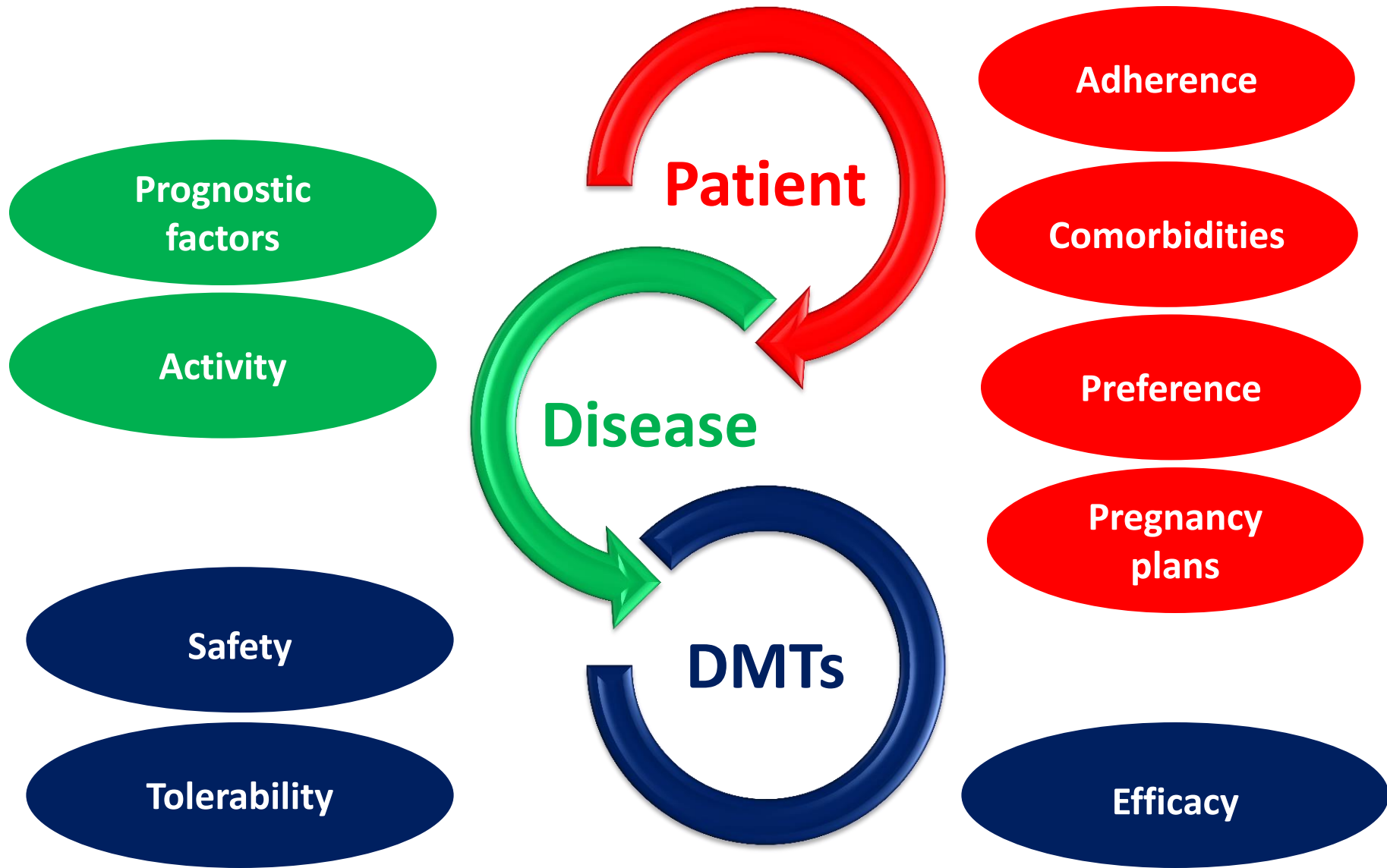
MS Comorbidities



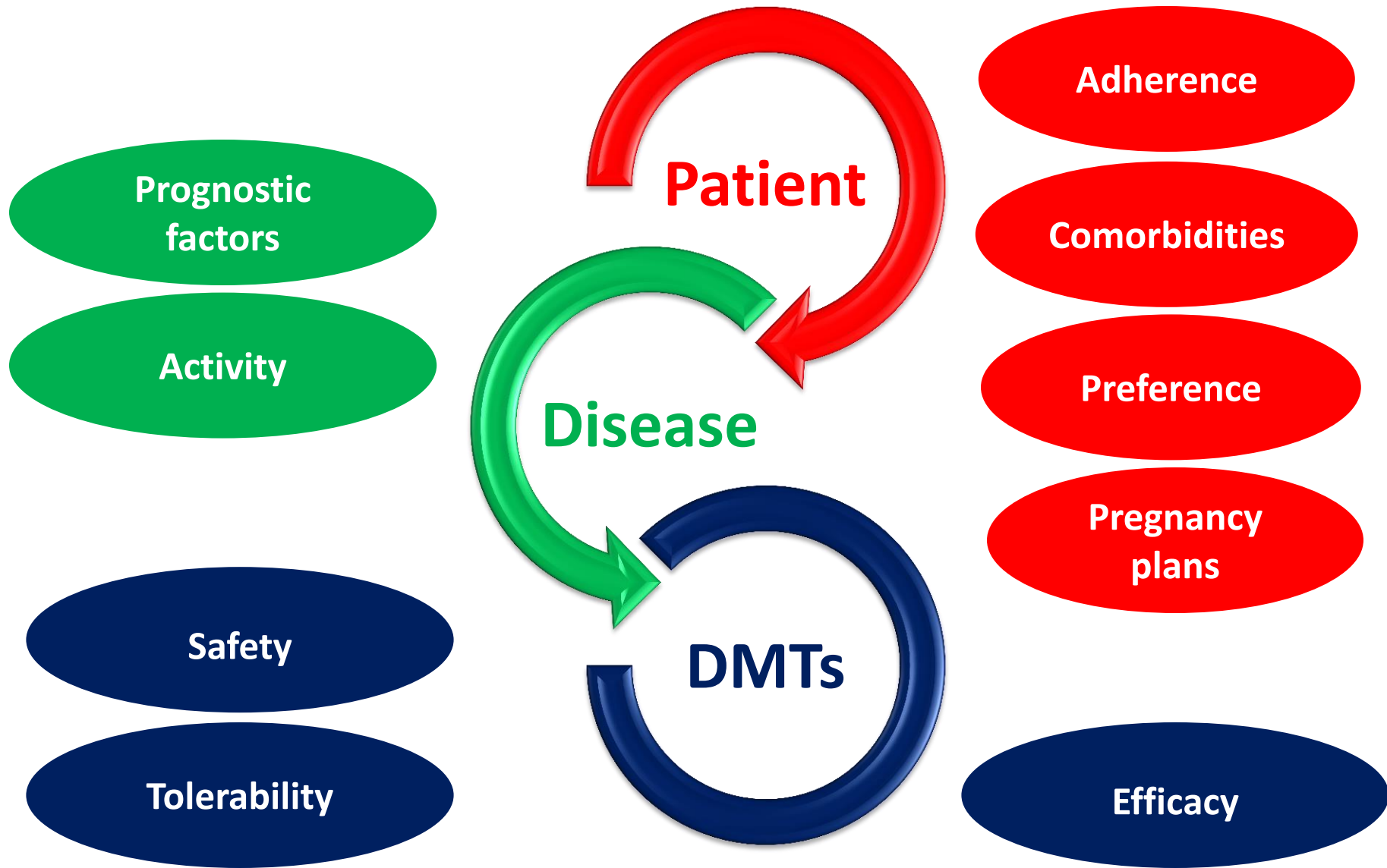
MS Comorbidities



Factors governing Choice of the 1st line therapy



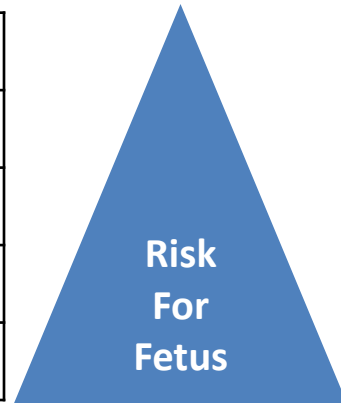
Factors governing Choice of the 1st line therapy



Pregnancy plans

Pregnancy Categories – US*

Category A	
Category B	Glatiramer Acetate
Category C	Interferons, Tysabri, Gilenya, Tecfidera
Category D	
Category X	Aubagio



Category X	Studies in animals or humans have demonstrated fetal abnormalities and/or there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience, and the risks involved in use of the drug in pregnant women clearly outweigh potential benefits.
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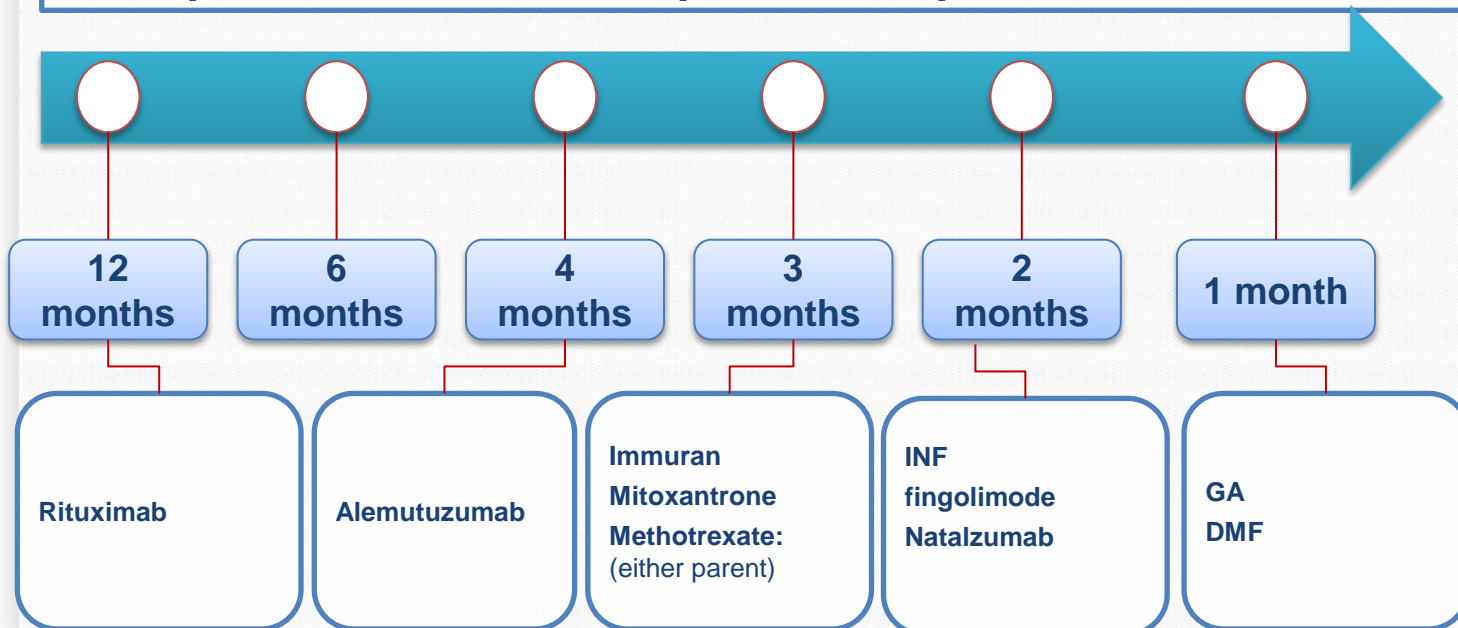
*Description in Notes Section

Depicted from <http://depts.washington.edu/druginfo/Formulary/Pregnancy.pdf> accessed March 14 2012, Category allocation according to US prescribing information of the respective products as of Nov 2012.

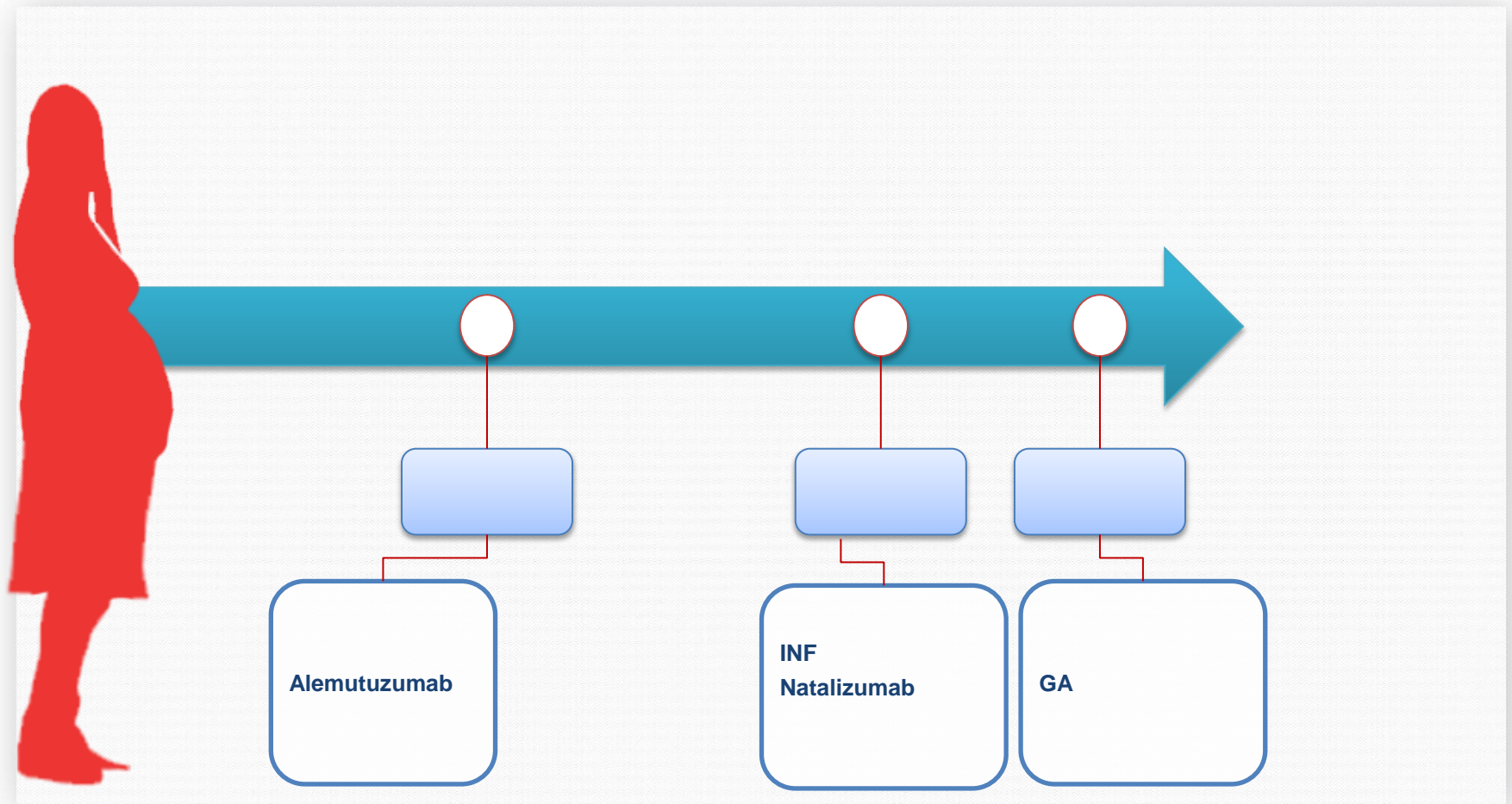
Pregnancy plans

Precautions before pregnancy.

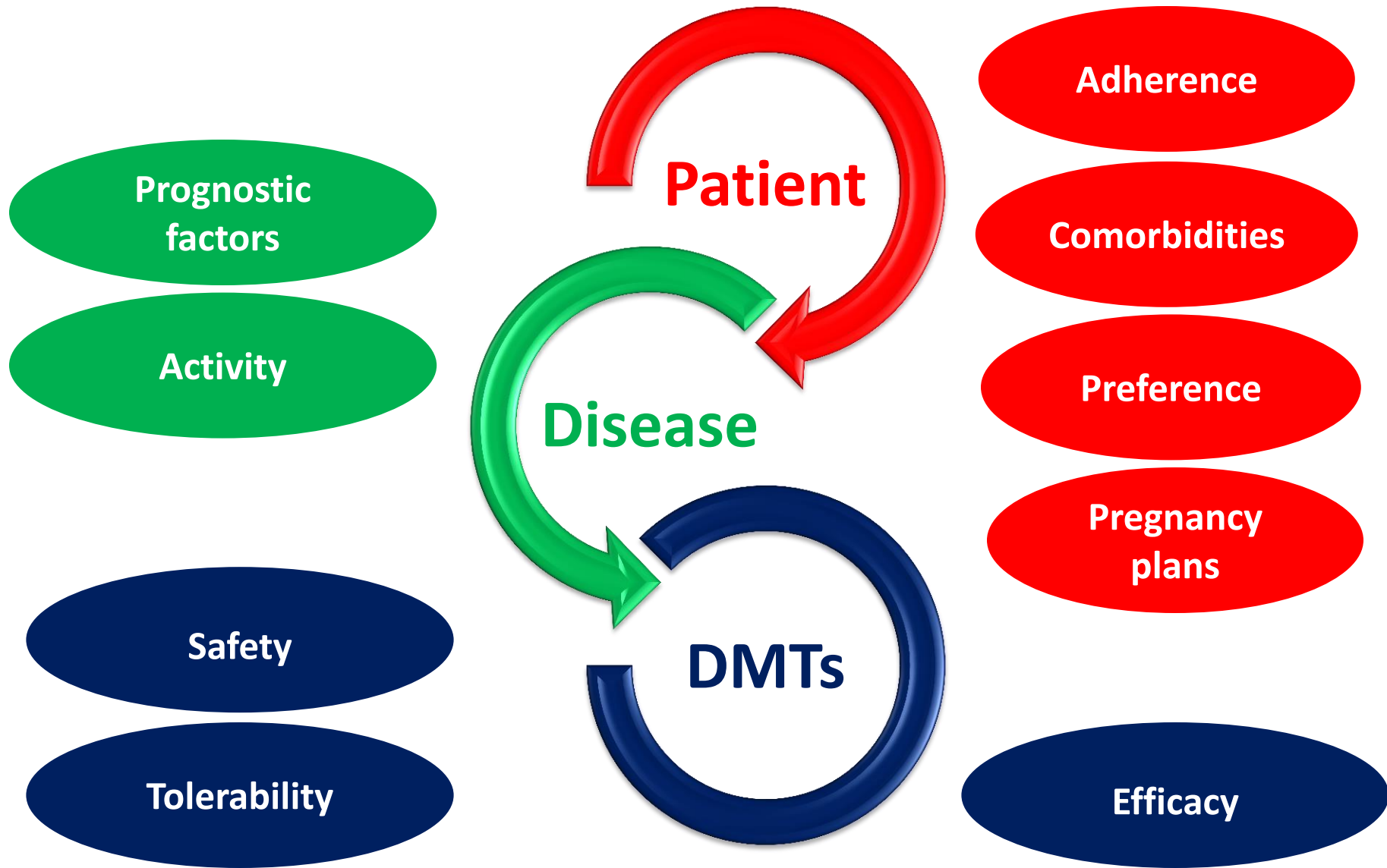
- Try to stabilize patient 6 months -1 year prior to trials of pregnancy (attack free + stable MRI).
- Stop DMDs before conception attempts



DMTs that can be used during pregnancy



Factors governing Choice of the 1st line therapy



Stratify individual patients based on risk of MS disability progression

GOOD	Epidemiological factors	BAD
Female	Sex	Male
< 40 y	Age	> 40 y

Stratify individual patients based on risk of MS disability progression

GOOD	RELAPSES	BAD
Mild, monofocal	1 st relapse	Severe , multifocal
Sensory, ON	Clinical presentation	Motor, cerebellar
Full recovery	Response to ttt	Residual
Long	Time to 2 nd relapse	Short
Low	Relapse rate	High

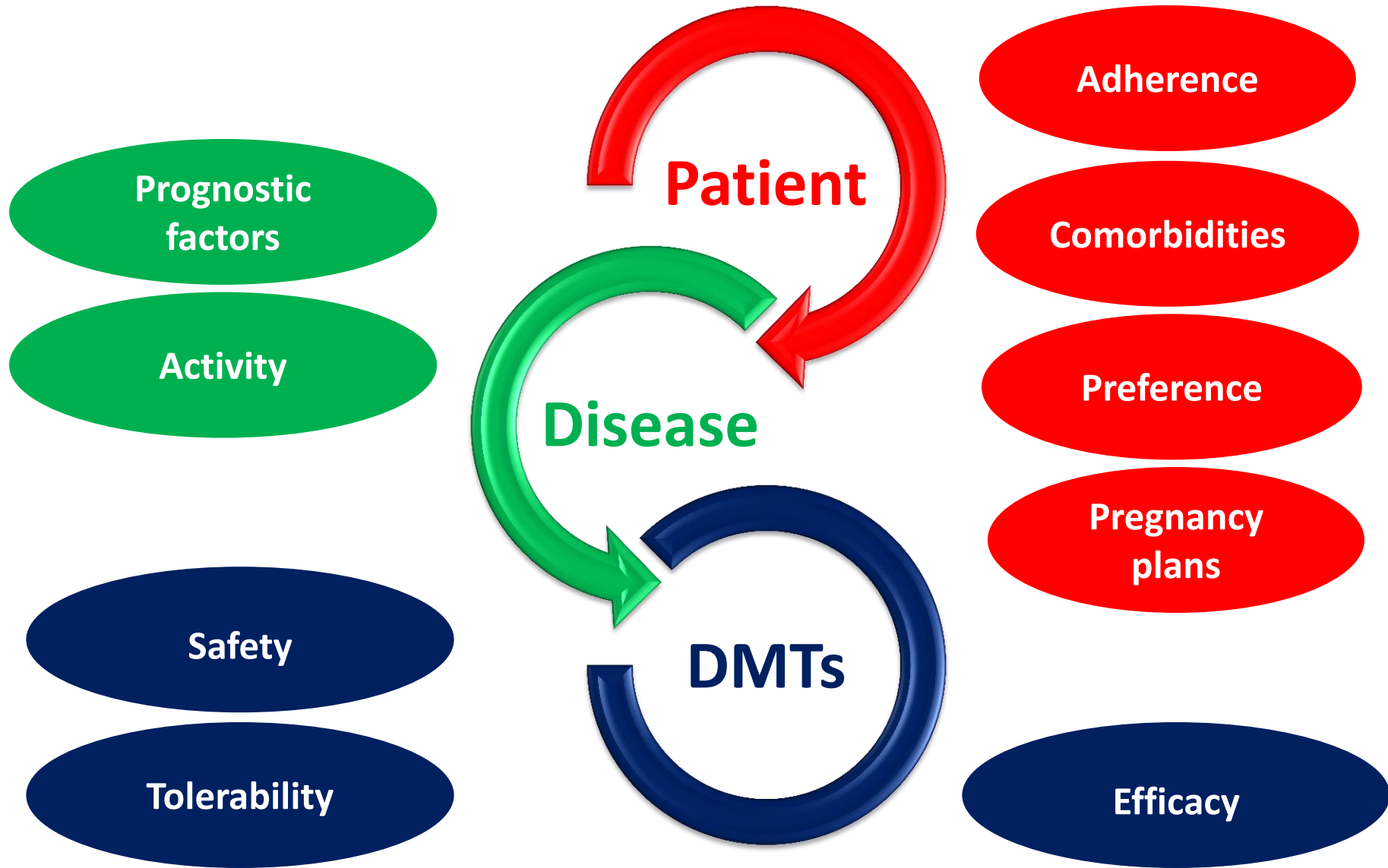
Stratify individual patients based on risk of MS disability progression

GOOD	DISABILITY	BAD
Long	Time to EDSS 4-5	Short

Stratify individual patients based on risk of MS disability progression

GOOD	MRI	BAD
Low	T2 Lesion load	High
Absent	CEL	Present
Absent	Black holes	Present
Absent	Infratentorial lesions	Present

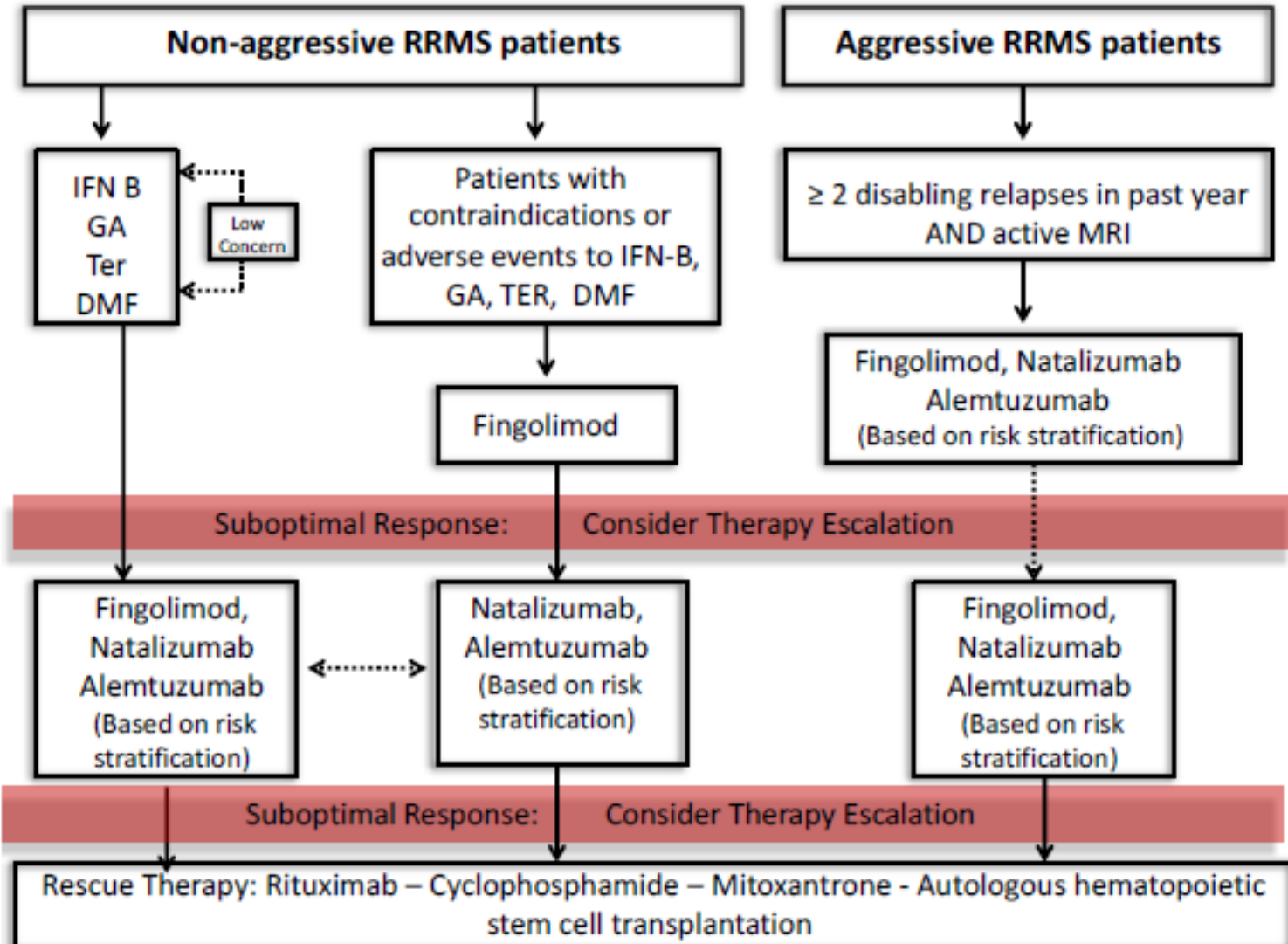
Factors governing Choice of the 1st line therapy



Definition of Highly active MS

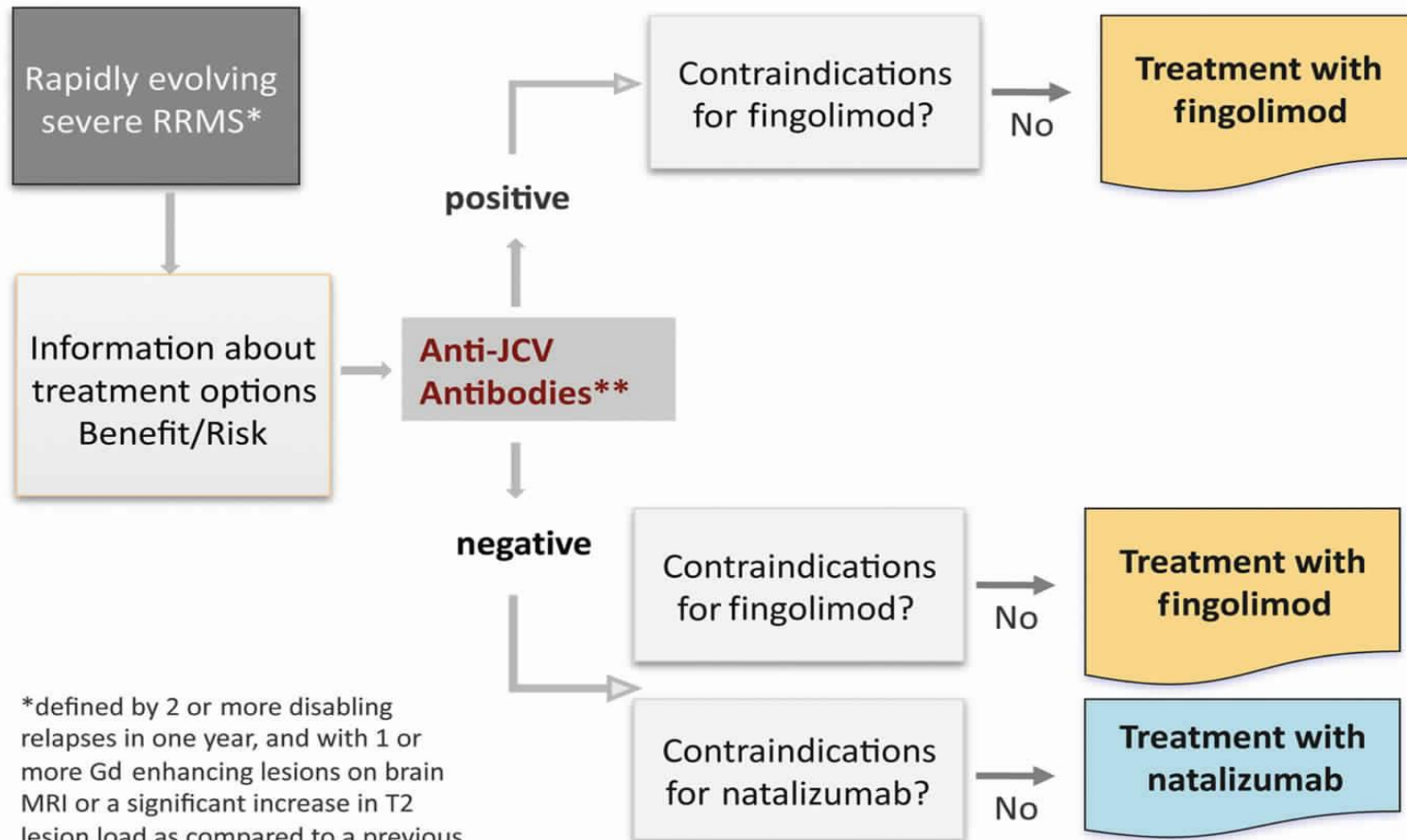
- EDSS score of 4.0 within 5 years of onset
- Poor response to at least 1 full year of therapy with one or more disease-modifying therapies, not because of intolerance
- Breakthrough disease over at least 1 year of disease-modifying therapy consisting of:
 - Two or more disabling relapses with incomplete resolution
 - Two or more MRI studies showing new or enlarging T2 lesions or gadolinium-enhancing lesions

MENACTRIMS Treatment recommendations



Treatment Algorithm

Treatment-naïve patients



*defined by 2 or more disabling relapses in one year, and with 1 or more Gd enhancing lesions on brain MRI or a significant increase in T2 lesion load as compared to a previous recent MRI

** as far it is available

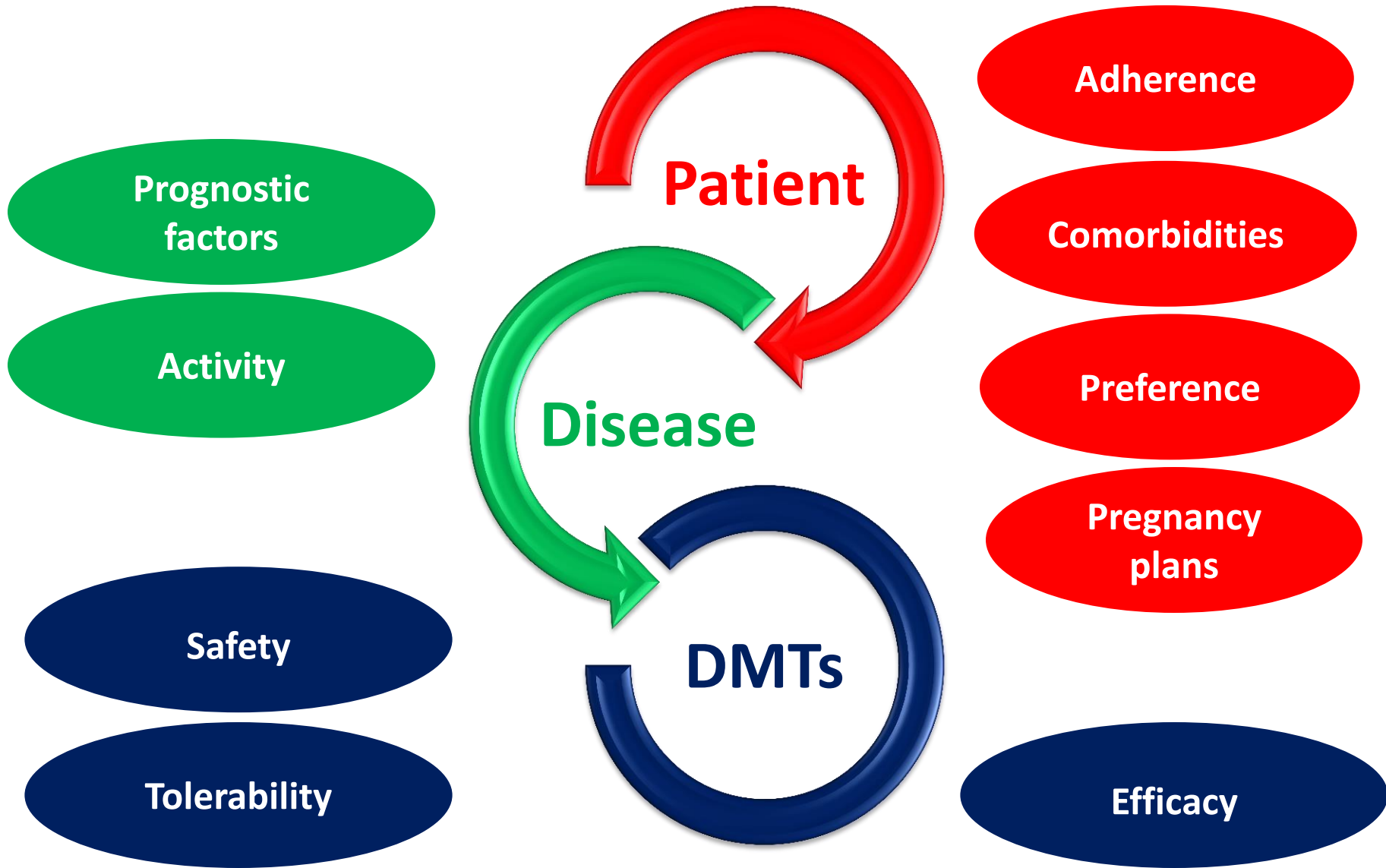
Practice guideline recommendations summary: Disease-modifying therapies for adults with multiple sclerosis

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Subcommittee of the American Academy of Neurology

Statement 14

Clinicians should prescribe alemtuzumab, fingolimod, or natalizumab for people with MS with highly active MS (Level B).

Factors governing Choice of the 1st line therapy

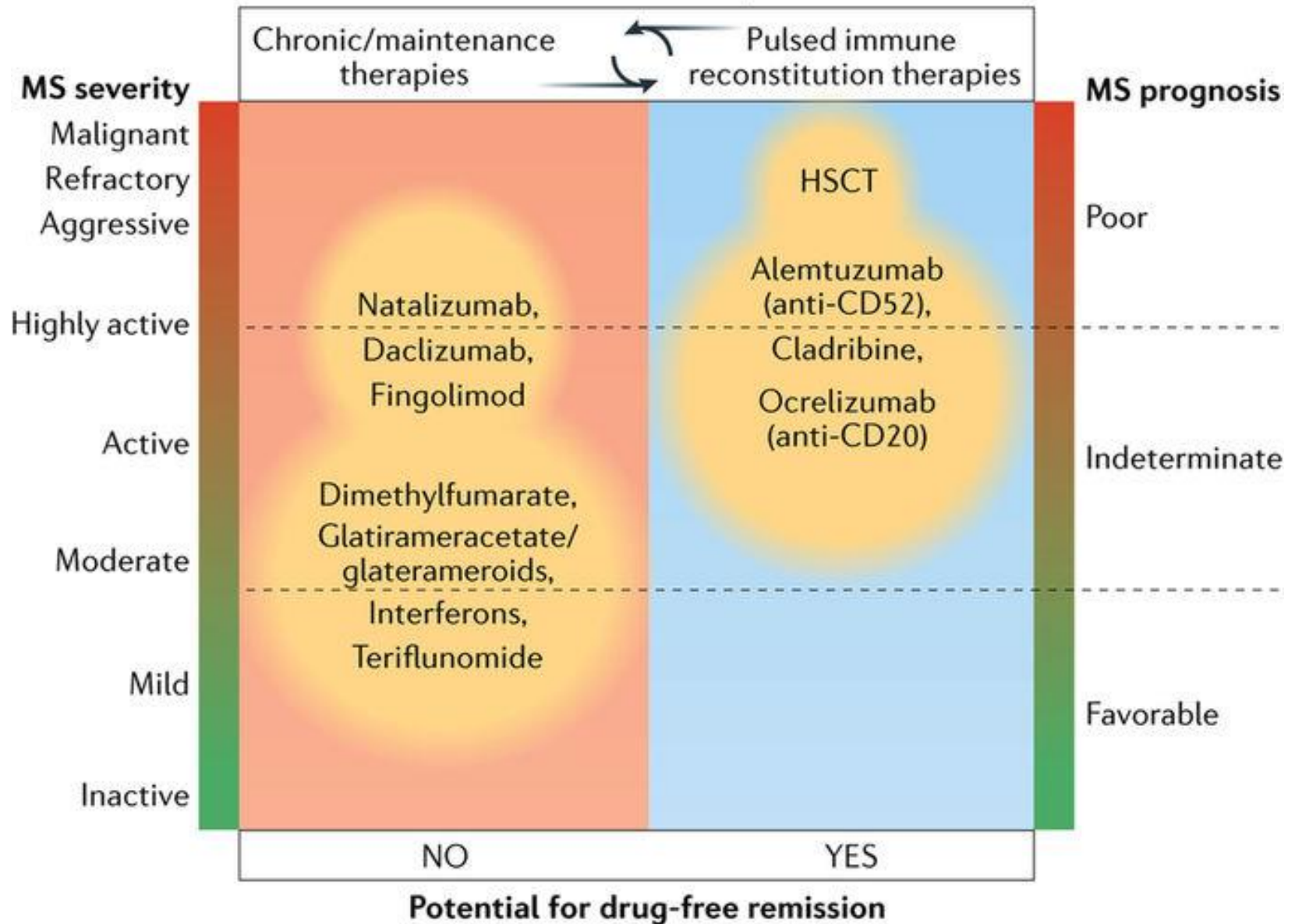


Comparative efficacy of oral therapies

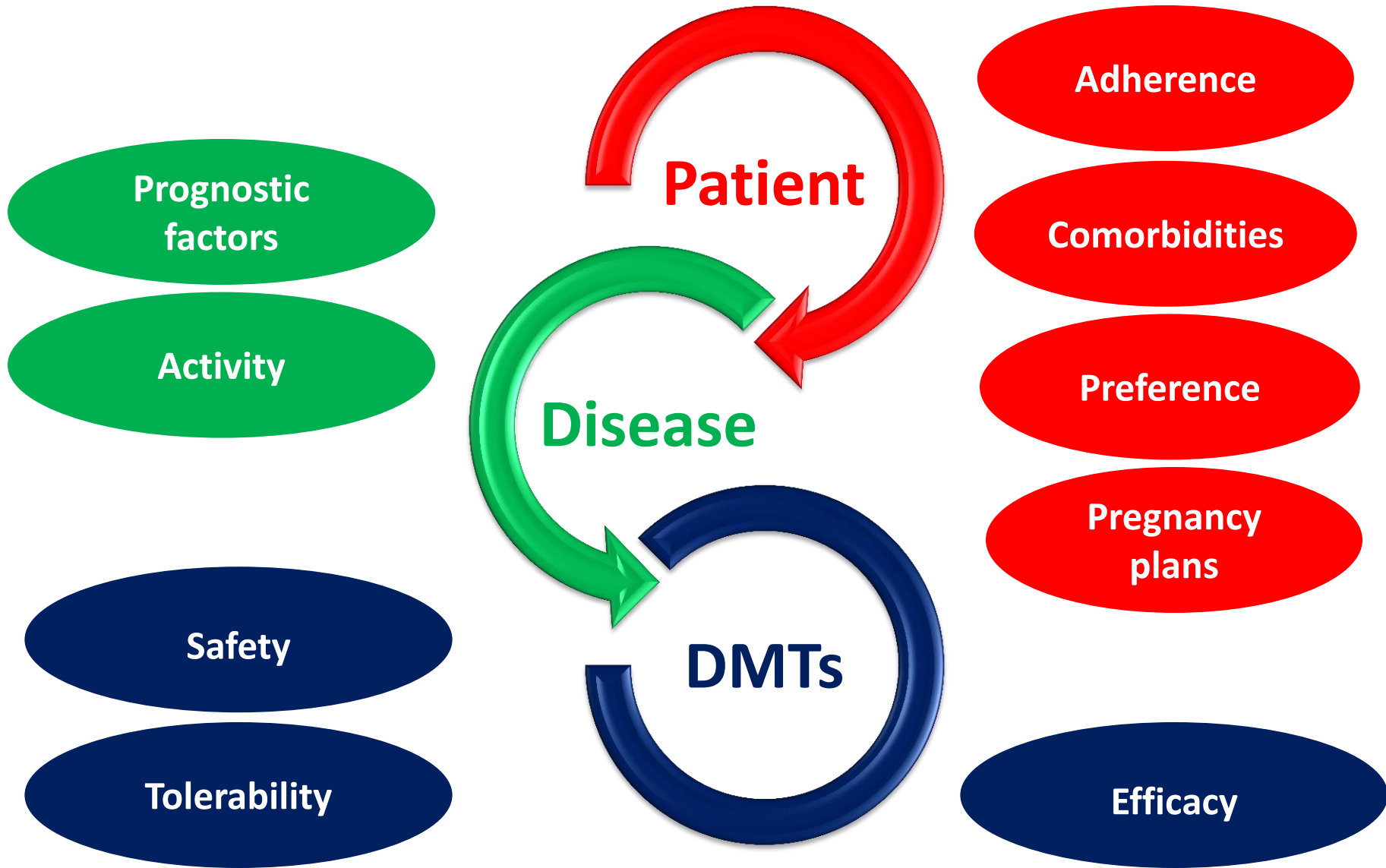
	Fingolimod		BG-12		Teriflunomide	
ARR	FREEDOMS	↓ 54% *	DEFINE	↓ 48% *	TEM SO	↓ 31%*
	TRANSFORMS	↓ 52% *				
	FREEDOMS II	↓ 48% *	CONFIRM	↓ 50% *	TOWER	↓ 36%*
Confirmed disability progression	FREEDOMS	↓ 30% *	DEFINE	↓ 34% *	TEM SO	↓ 30%*
	TRANSFORMS	↓ 29%				
	FREEDOMS II	↓ 17%	CONFIRM	↓ 24%	TOWER	↓ 31%*

* P < 0.05

Treatment concept



Factors governing Choice of the 1st line therapy

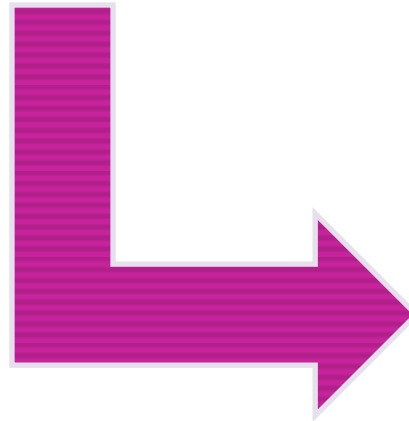


Treatment options

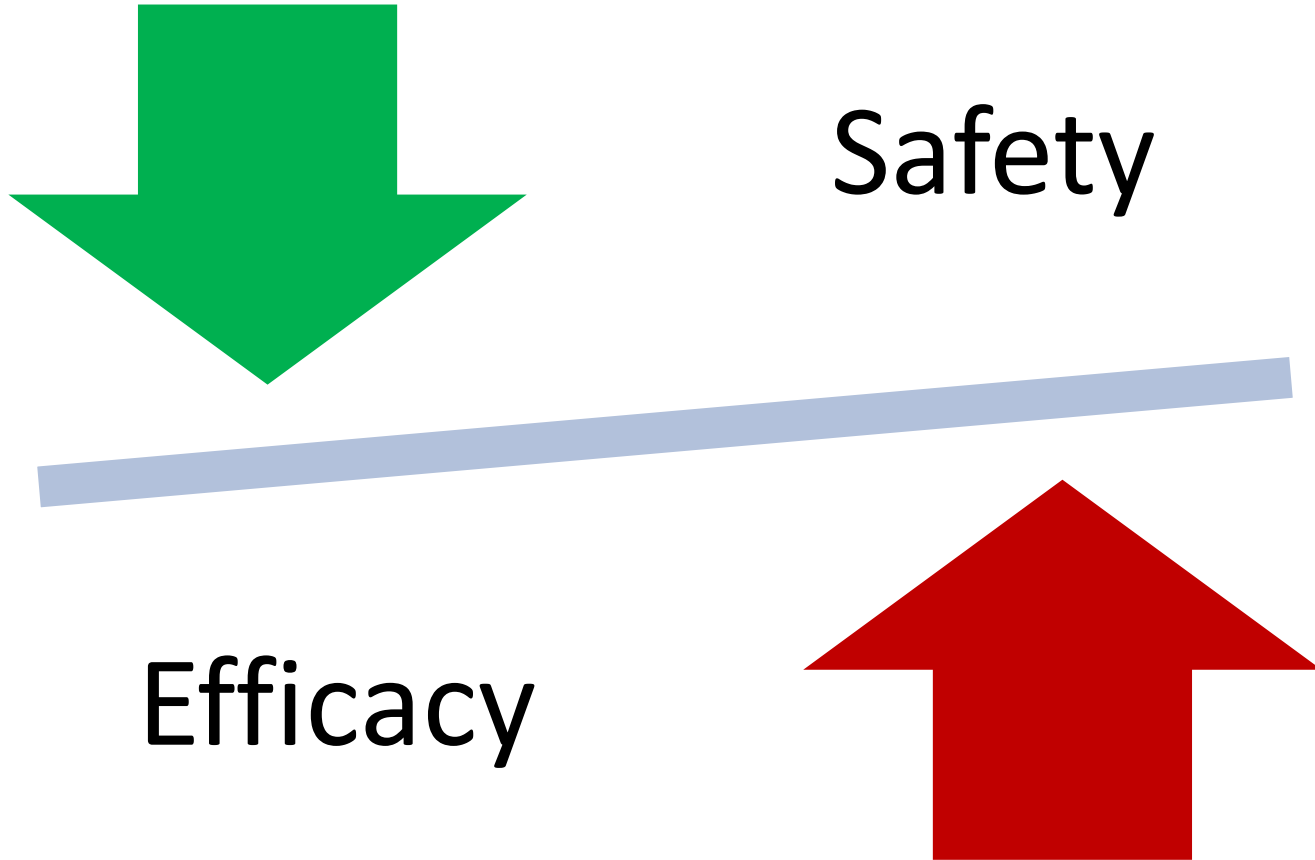
**Immune Reconstitution
Therapy**

**Chronic
Immunosuppression**

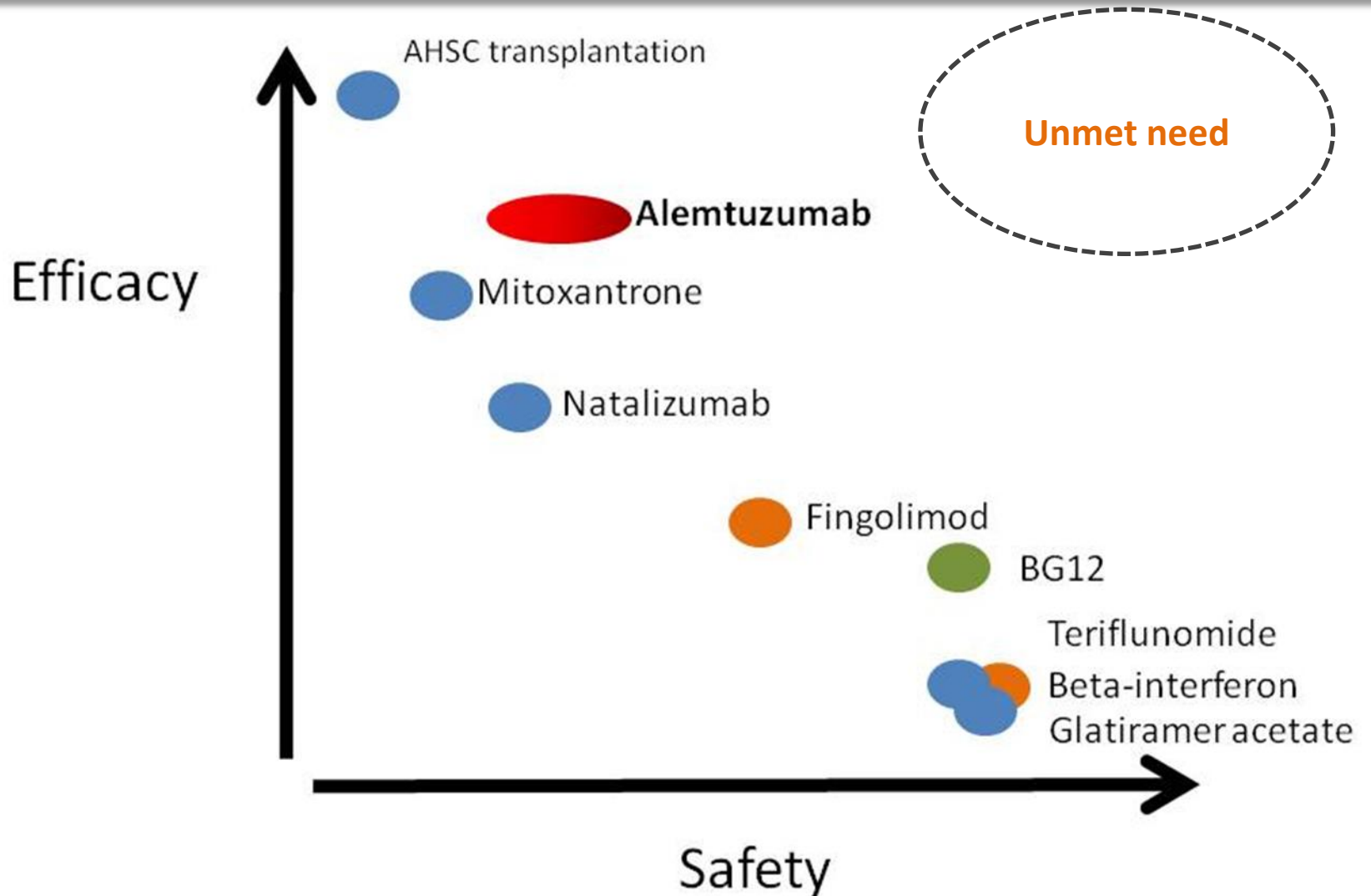
Immunomodulation



Efficacy **Vs** Safety



Efficacy Vs Safety

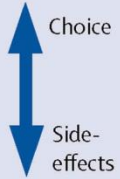


Treatment Algorithm

Initial choice of therapy

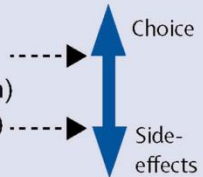
Patients with average active MS

Dimethyl fumarate
Teriflunomide*
Interferon beta and
glatiramer acetate



Patients with aggressive MS

Natalizumab
JC virus Ab-
JC virus Ab+ (high)
JC virus Ab+ (low)
Fingolimod
Alemtuzumab
Daclizumab

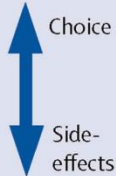


Treatment Algorithm

Initial choice of therapy

Patients with average active MS

Dimethyl fumarate
Teriflunomide*
Interferon beta and
glatiramer acetate



Suboptimal effect

Escalation of therapy

Natalizumab

JC virus Ab-

JC virus Ab+ (high)

JC virus Ab+ (low)

Fingolimod

Alemtuzumab

Choice

Side-effects

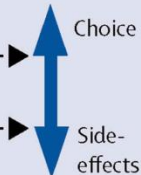
Sub-optimal effect

Suboptimal effect

Mitoxantron†

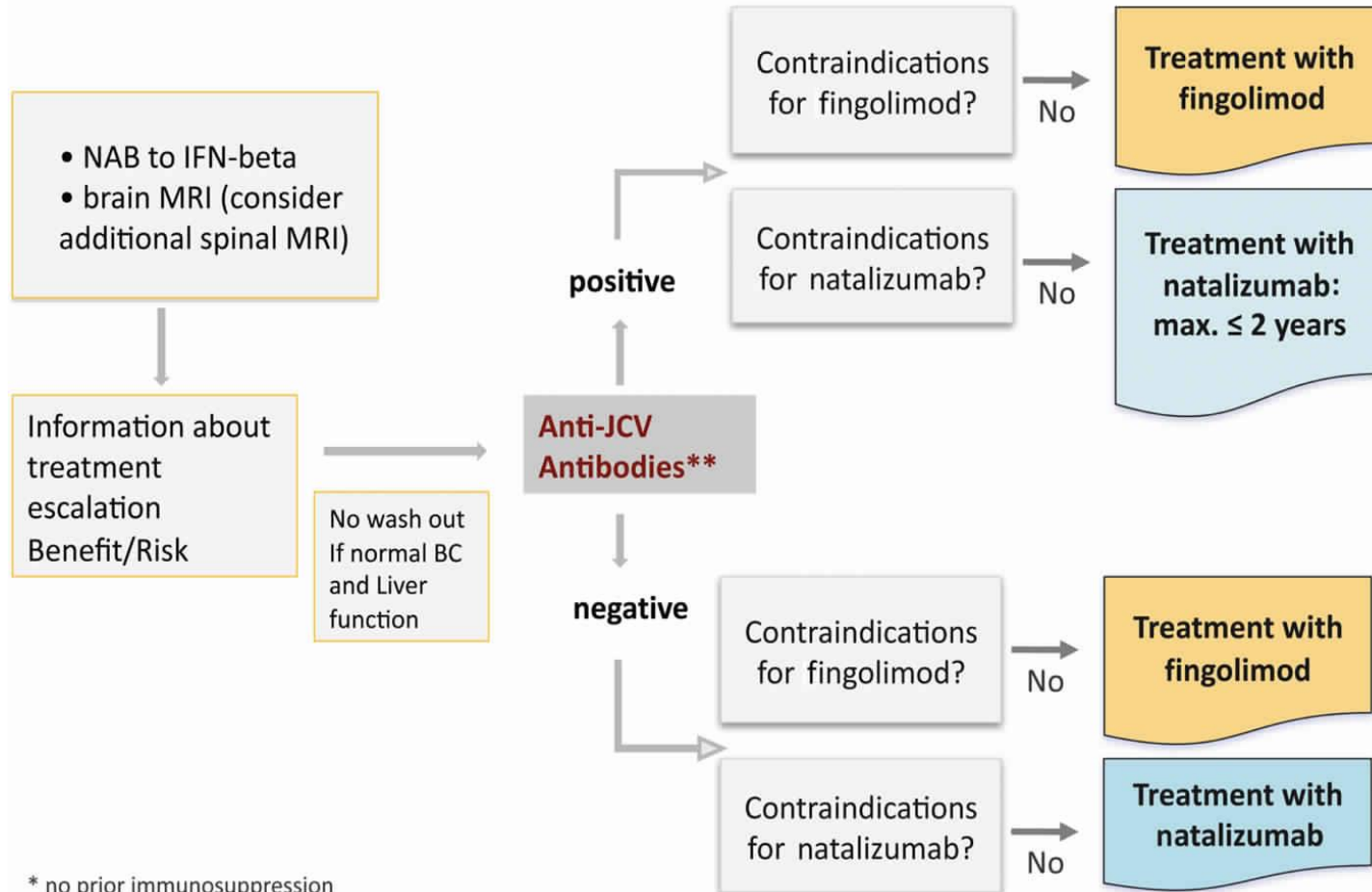
Patients with aggressive MS

Natalizumab
JC virus Ab-
JC virus Ab+ (high)
JC virus Ab+ (low)
Fingolimod
Alemtuzumab
Daclizumab



Treatment Algorithm

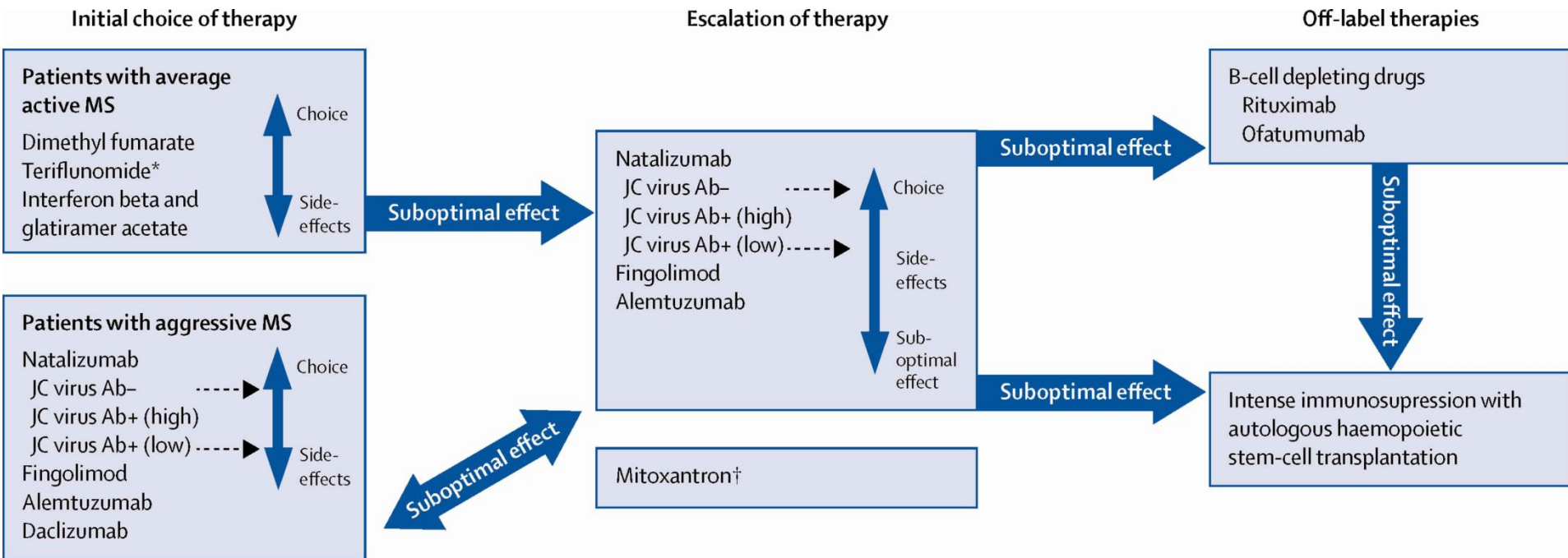
Non-responder to IFN-beta* or GA*



* no prior immunosuppression

** as far it is available

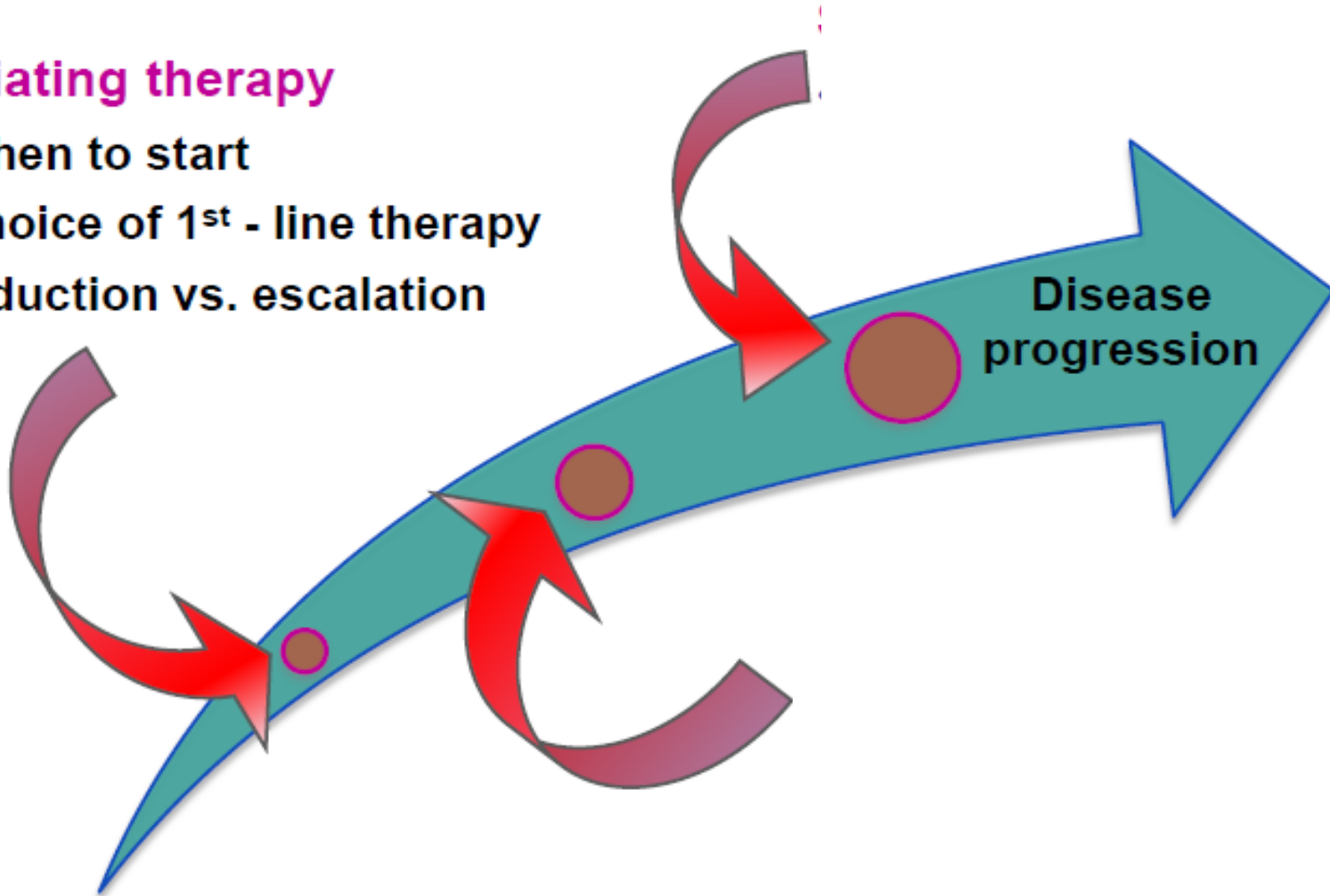
Treatment Algorithm



Key decision making points in Treatment of MS

Initiating therapy

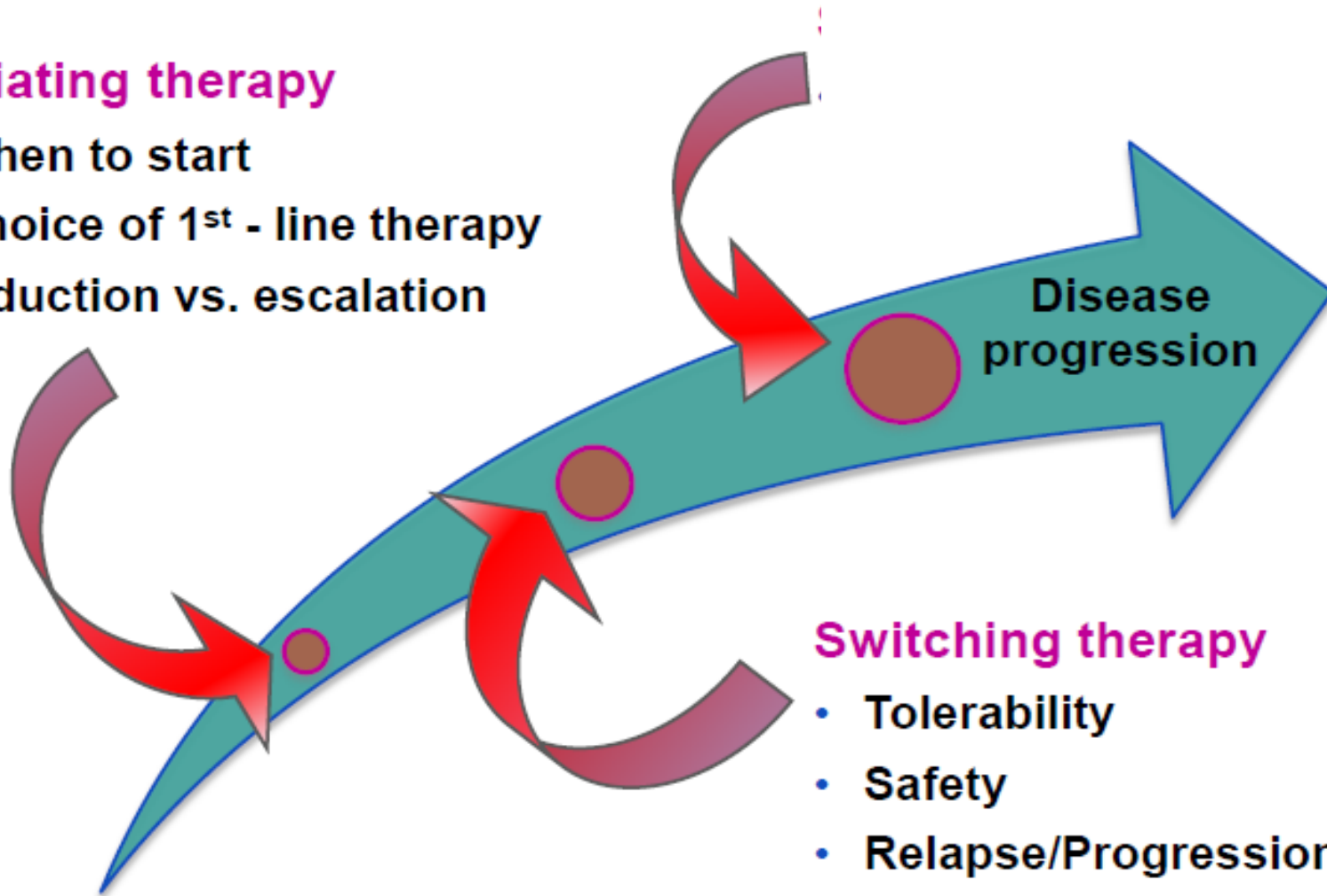
- When to start
- Choice of 1st - line therapy
- Induction vs. escalation



Key decision making points in Treatment of MS

Initiating therapy

- When to start
- Choice of 1st - line therapy
- Induction vs. escalation



Switching therapy

- Tolerability
- Safety
- Relapse/Progression/MRI

Definition of suboptimal response

Relapse



Disability



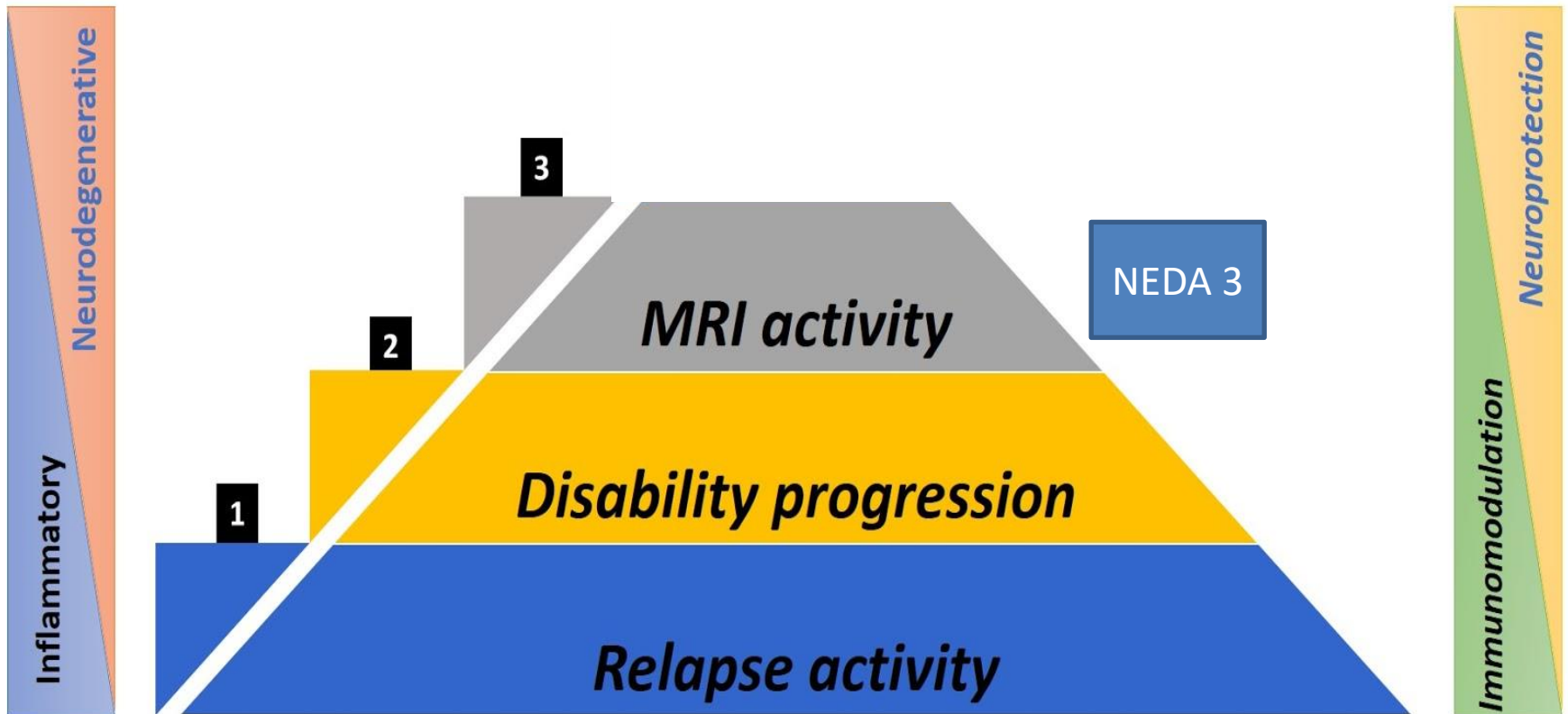
MRI



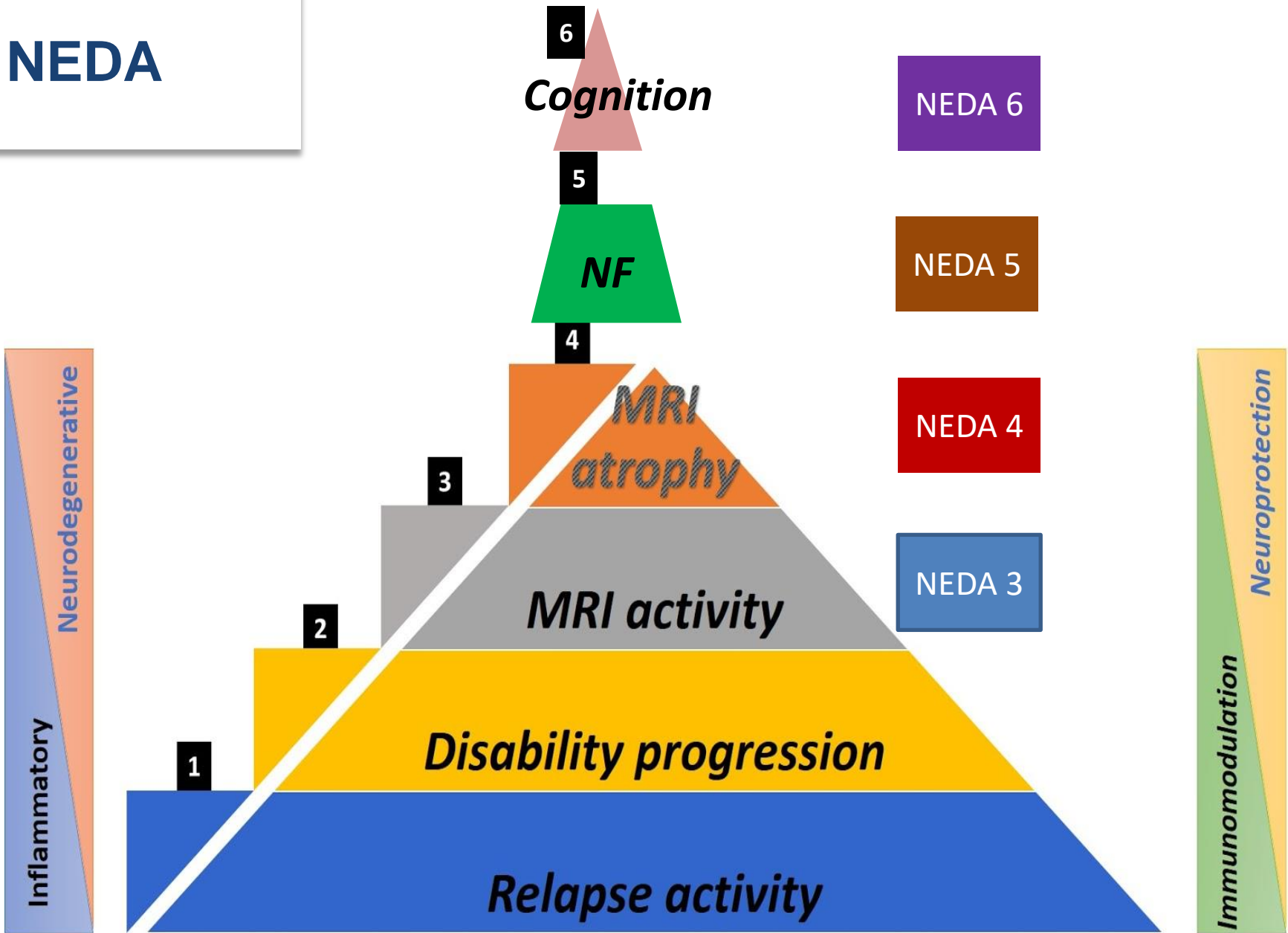
NEDA

No Evidence of Disease activity

NEDA



NEDA



Definition of suboptimal response

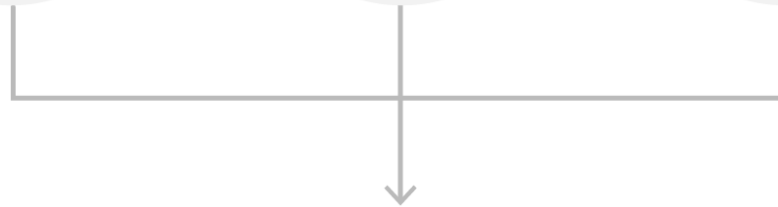
Relapse



Disability



MRI



NEDA

No Evidence of Disease activity

Definition of suboptimal response

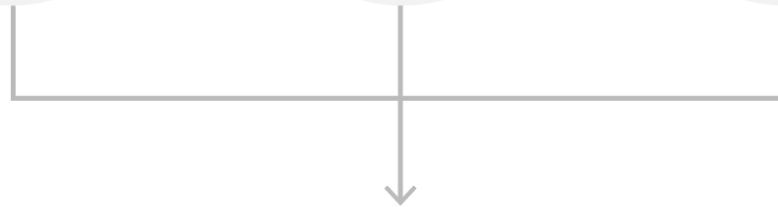
Relapse



Disability



MRI



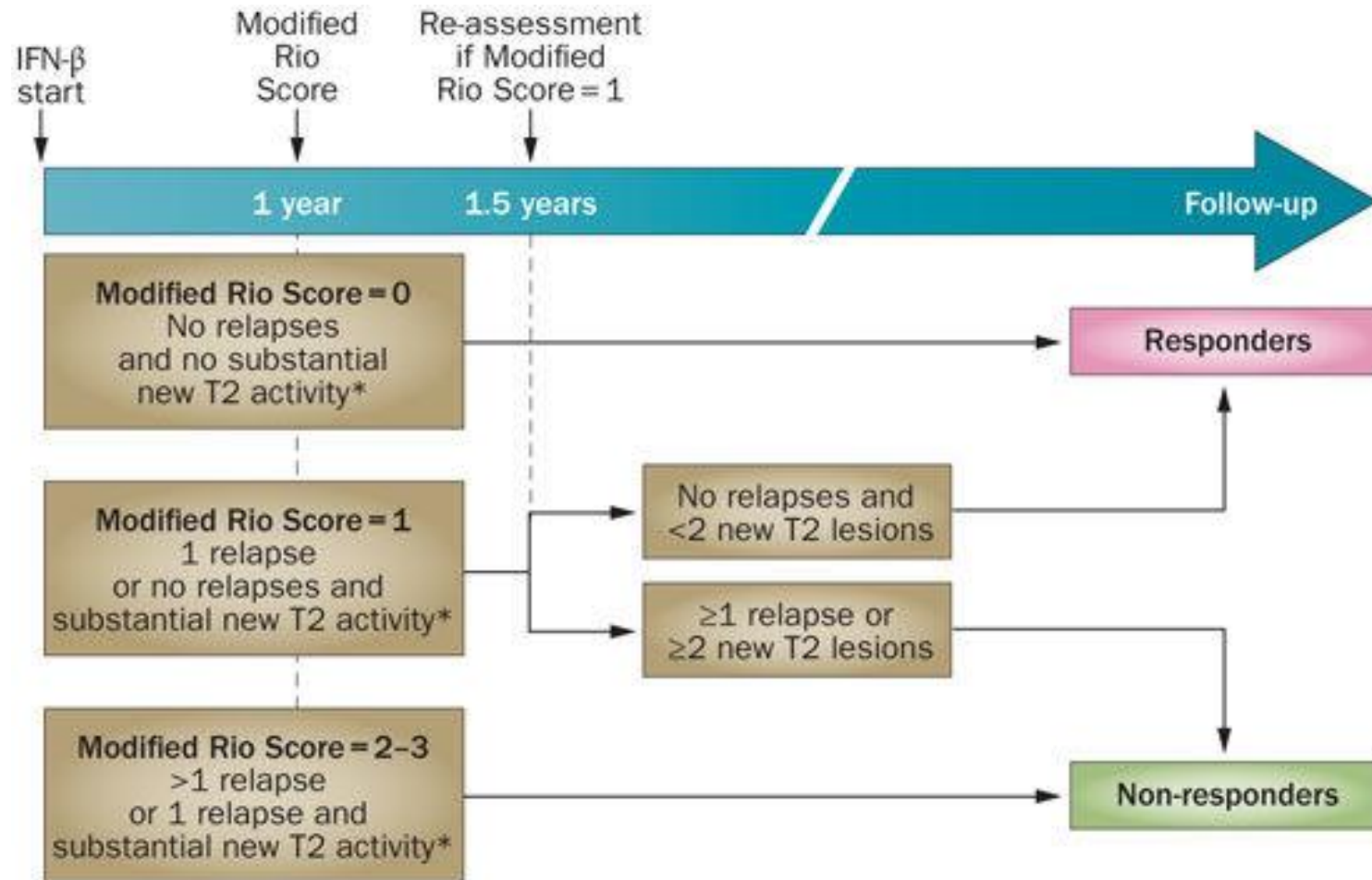
MEDA

Minimal Evidence of Disease activity

Rio score

Rio Score	
Criterion	Change over the first year
MRI criterion = 0	≤ 2 active* T2 lesions
MRI criterion = 1	> 2 active T2 lesions
Relapse criterion = 0	No relapses
Relapse criterion = 1	≥ 1 relapse
EDSS criterion = 0	Increase in EDSS score of < 1 point
EDSS criterion = 1	Increase in EDSS score of ≥ 1 point, sustained over at least 6 months

Rio score



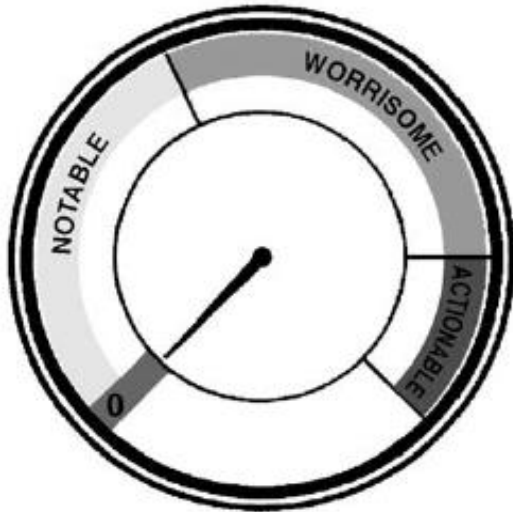
Modified Rio score

Criterion	Change over 1 st year	Score
MRI	≤ 4 (5) [‡] new T2 lesions	0
	> 4 (5) [‡] new T2 lesions	1
Relapse	No relapses	0
	1 relapse	1
	≥ 2 relapses	2

Score =
MRI criterion + relapse criterion

‡The cut-off of 4 lesions applied to the validation set;
the cut-off of 5 lesions applied to the training set.

Canadian Optimization Protocol



Relapse



Progression



MRI

Determining the level of concern to consider treatment modification based on relapse outcomes

	Low	Medium	High
Rate	1 attack in 2 nd yr Tx	1 attack in 1 st yr Tx	> 1 attack in 1 st year of Tx
Severity	Mild <ul style="list-style-type: none"> ● No Steroids ● Min effect on ADL ● 1 FS involved ● No motor/cerebellar involvement 	Moderate <ul style="list-style-type: none"> ● Steroids required ● Mod effect on ADL ● >1 FS involved ● Moderate motor/cerebellar involvement 	Severe <ul style="list-style-type: none"> ● Steroids/hospital ● Severe effect on ADL ● >1 FS involved ● Severe motor/cerebellar involvement
Recovery	Prompt	Incomplete at 3 mths	Incomplete at 6 mths

Note:

1. It is best to examine patients with more severe attacks
2. Recovery requires a re-examination at specific timepoints
3. Cognitive only attacks are hard to objectively define

Determining the level of concern to consider treatment modification based on progression outcomes

Baseline EDSS	Low	Medium	High
≤3.5	<ul style="list-style-type: none"> • <2 points 	<ul style="list-style-type: none"> • 2 points confirmed at 3 mths 	<ul style="list-style-type: none"> • >2 points confirmed at 6 mths • 2 points confirmed at 1 year
4–5	<ul style="list-style-type: none"> • <1 point 	<ul style="list-style-type: none"> • 1 point confirmed at 6 mths 	<ul style="list-style-type: none"> • >1 point confirmed at 6 mths • 1 point confirmed at 1 year
≥5.5		<ul style="list-style-type: none"> • 0.5 points confirmed at 6 mths 	<ul style="list-style-type: none"> • >0.5 points confirmed at 6 mths
Clinically documented progression	<ul style="list-style-type: none"> • No motor Minor sensory 	<ul style="list-style-type: none"> • Some motor, cerebellar or cognitive • Multiple domains affected 	<ul style="list-style-type: none"> • Pronounced motor, cerebellar, or cognitive • Multiple domains affected
T25FW*	<ul style="list-style-type: none"> • ≤ 20% confirmed 6 mths 	<ul style="list-style-type: none"> • > 20% and < 100% increase confirmed 6 mths 	<ul style="list-style-type: none"> • ≥ 100% increase confirmed 6 mths

*T25FW tested at baseline with aid if required

Determining the level of concern to consider treatment modification based on MRI outcomes

Change in MRI Categories	Low	Medium	High
Gd-enhancing lesions	1 lesion	2 lesions	≥ 3 lesions
New T2 lesions (per year)*	1 lesion	2 lesions	≥ 3 lesions

*There must be confidence that lesions are truly “new” compared to previous scans

Note:

1. Routine follow-up MRI is recommended 6-12 months after initiating therapy (or in CIS if therapy is not initiated)
2. New T2 lesions that are also enhancing on the same scan are only counted once as unique active lesions

Baseline study should be performed when patient is stable and enough time has elapsed to expect that treatment is effective

Definition of suboptimal response

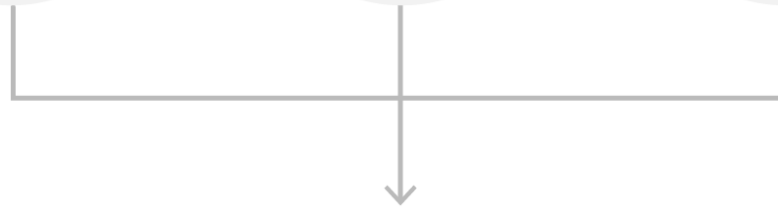
Relapse



Disability



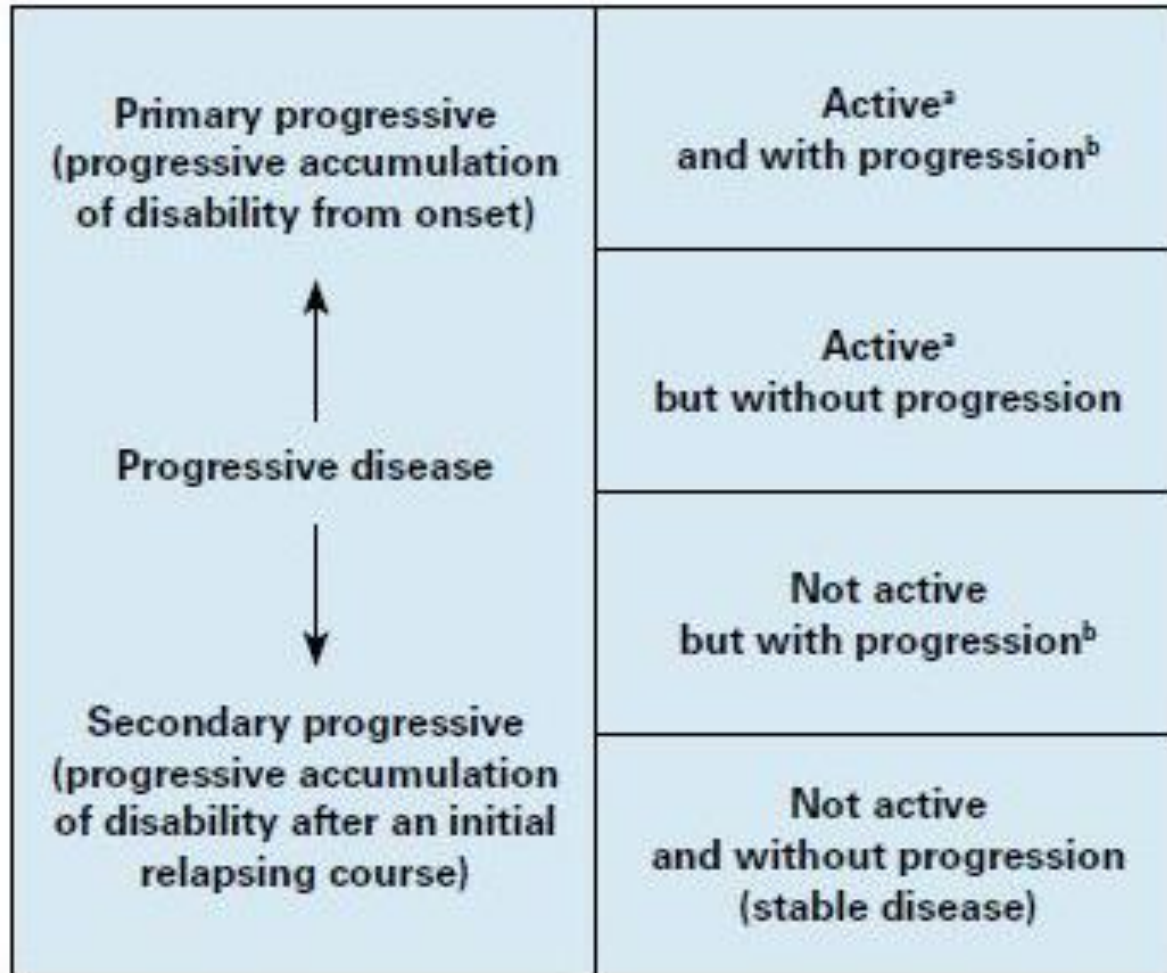
MRI



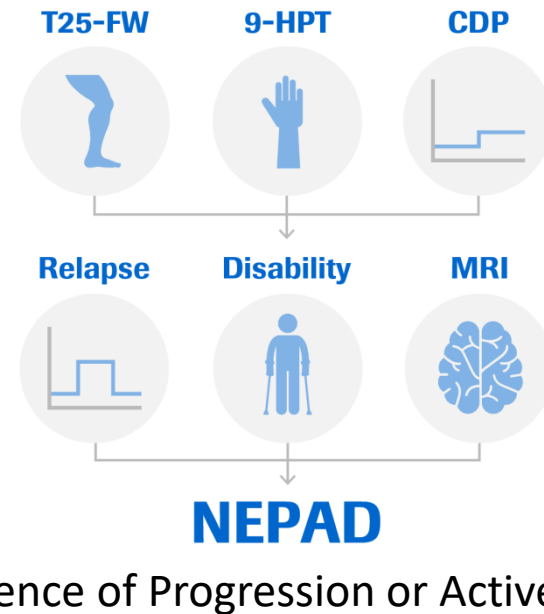
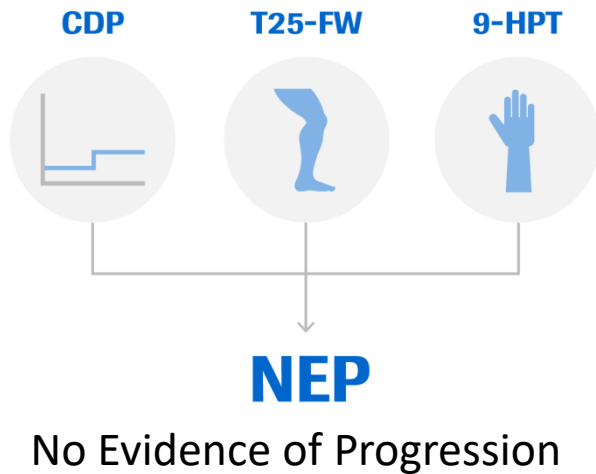
NEDA

No Evidence of Disease **activity**

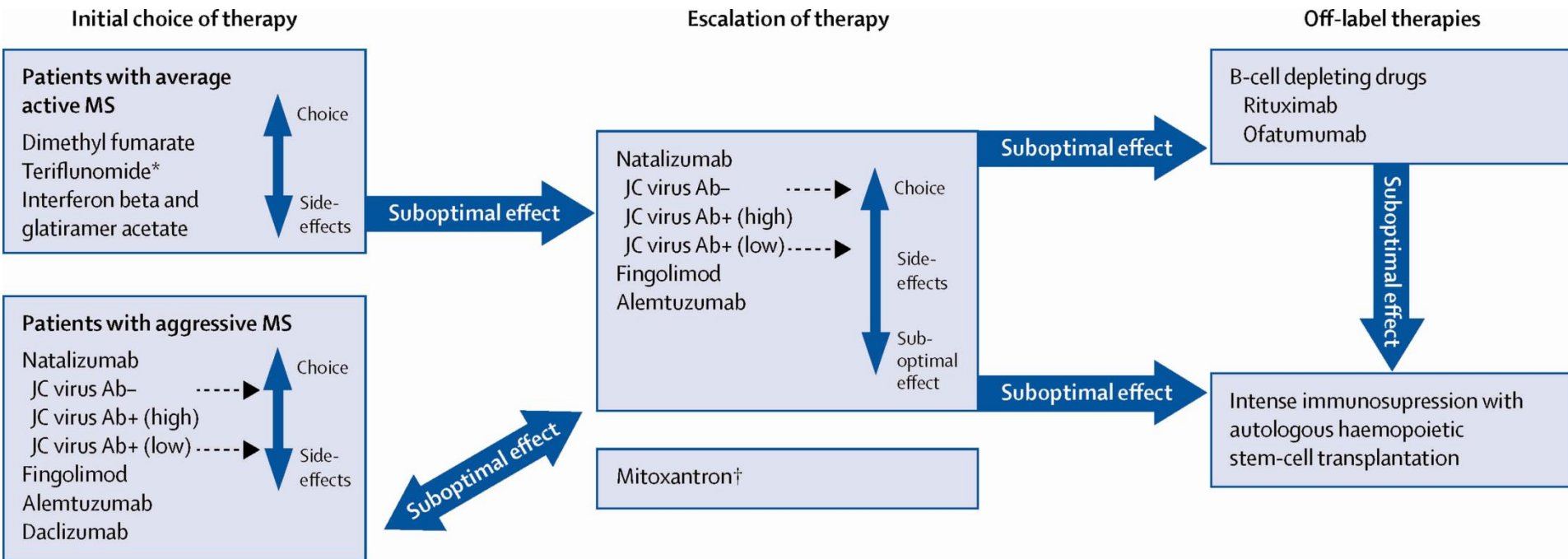
Definition of suboptimal response



Definition of suboptimal response



Treatment Algorithm



Escalation Vs Induction



Controversies in Multiple Sclerosis

Multiple sclerosis should be treated using a step-down strategy rather than a step-up strategy—YES

Gavin Giovannoni

Multiple Sclerosis Journal

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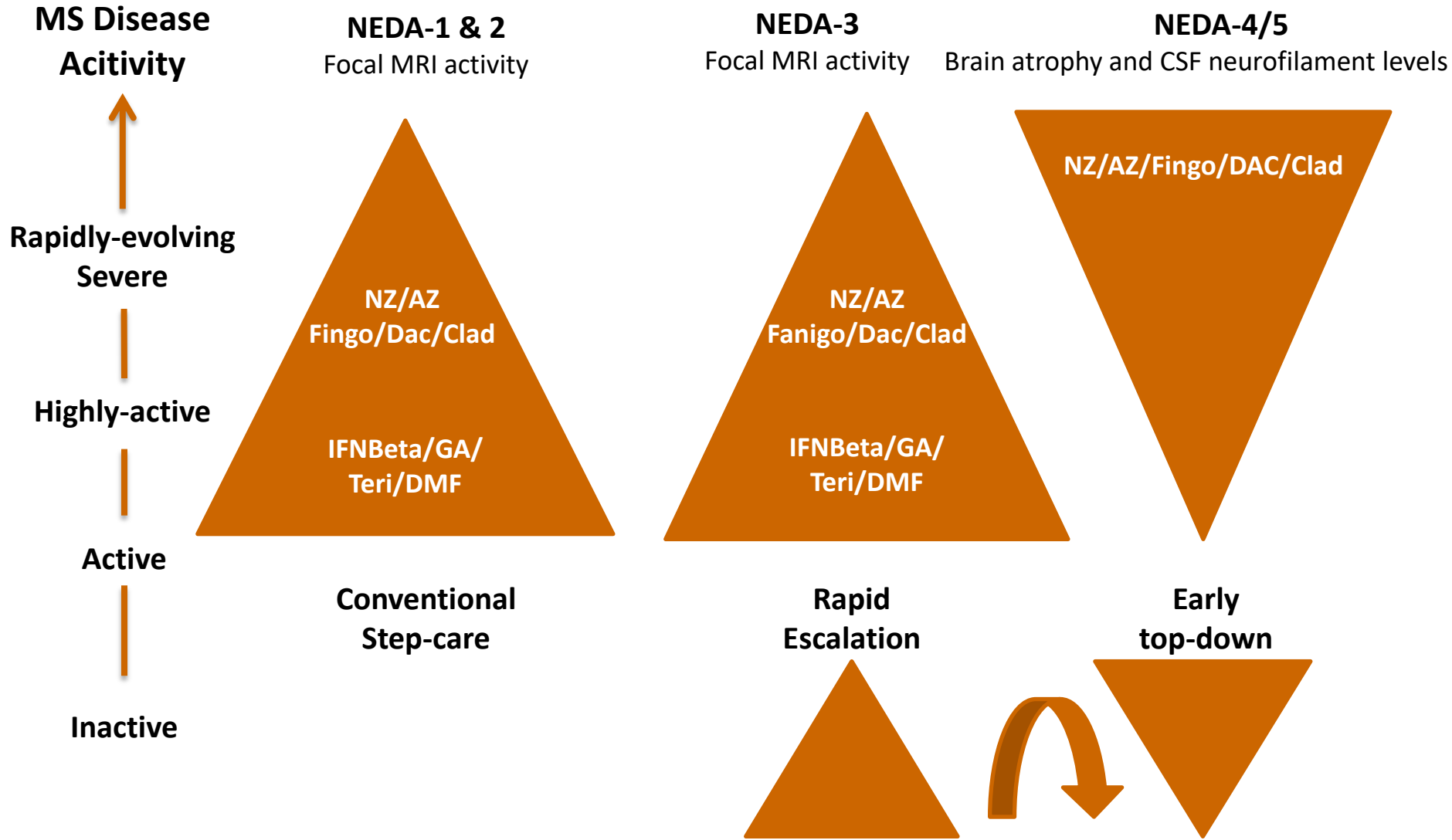
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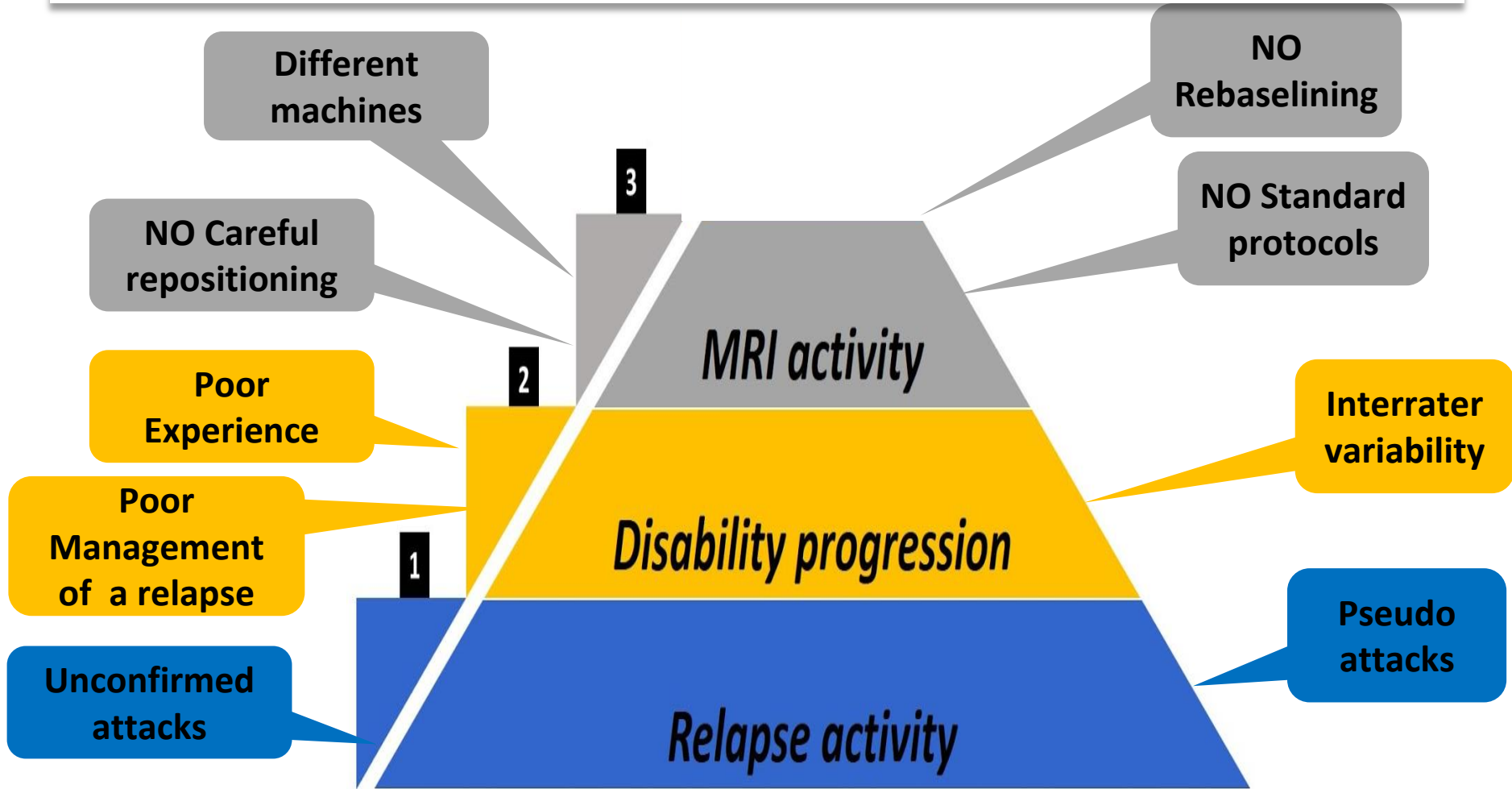
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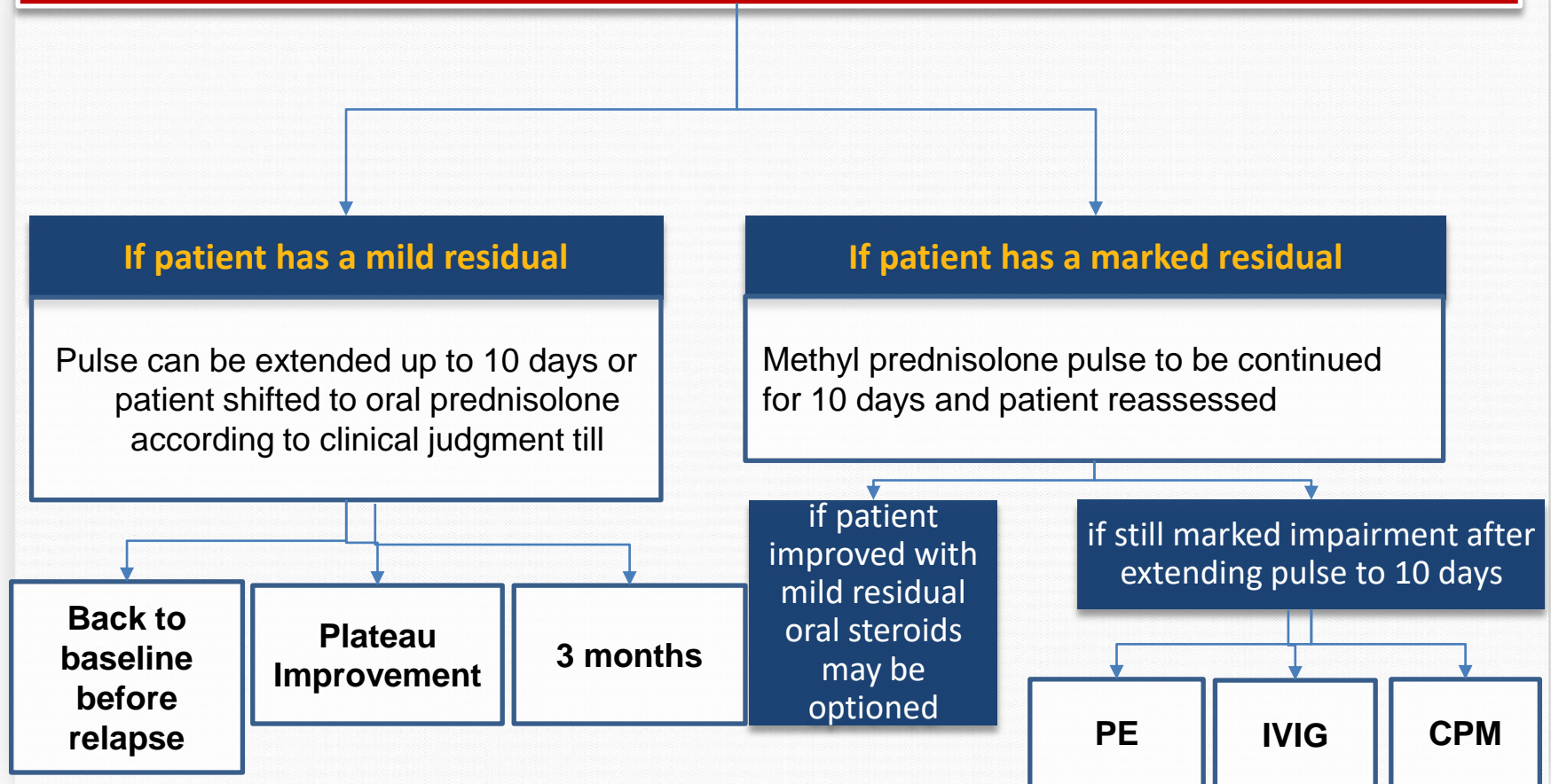
Flipping the pyramid in MS

Unjustified escalation

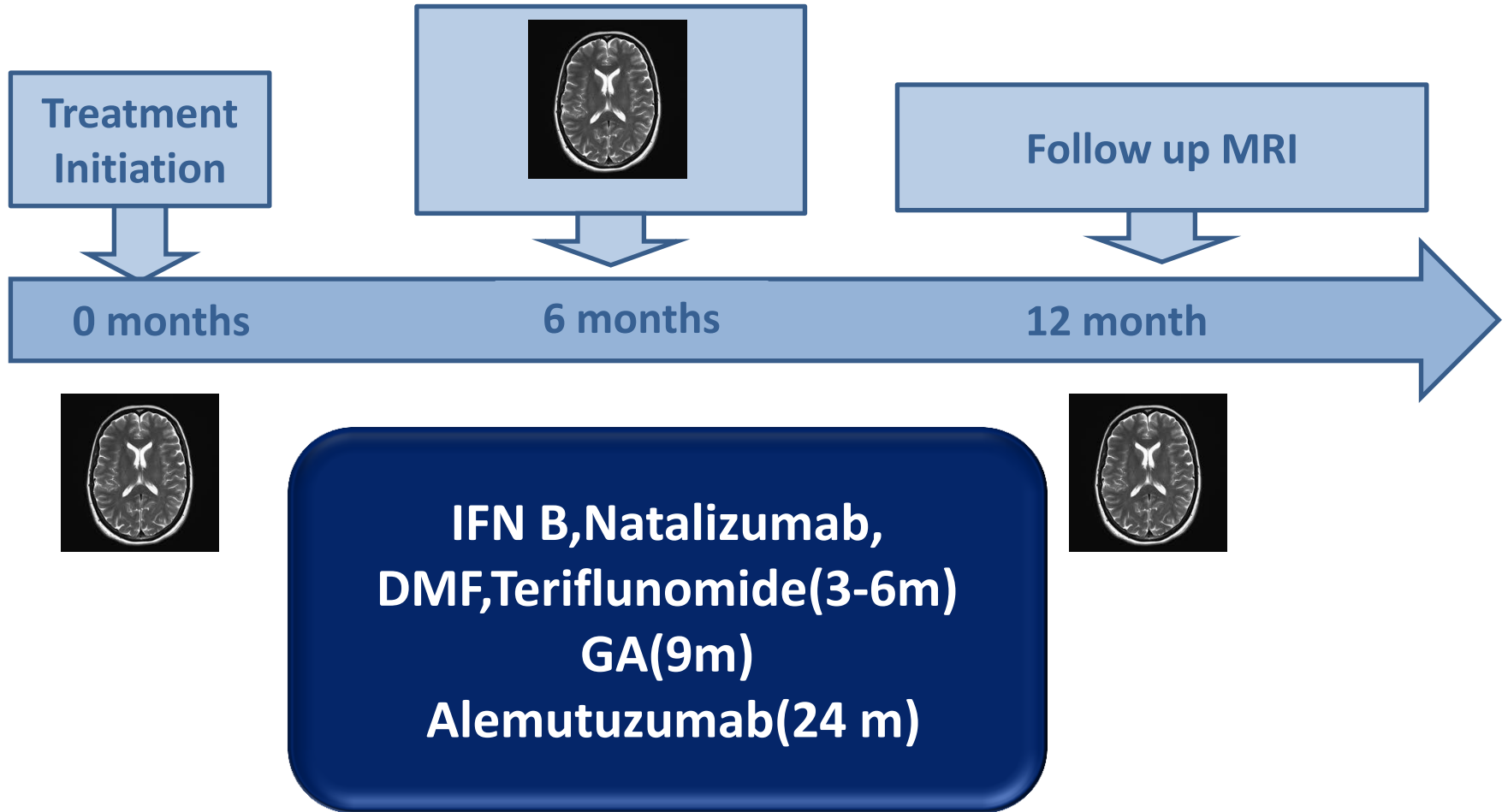


Algorithmic treatment of an attack

IV methyl prednisolone pulse 1 gm/day for 3-5 days then reassess after last dose



Rebaselining



Key decision making points in Treatment of MS

Initiating therapy

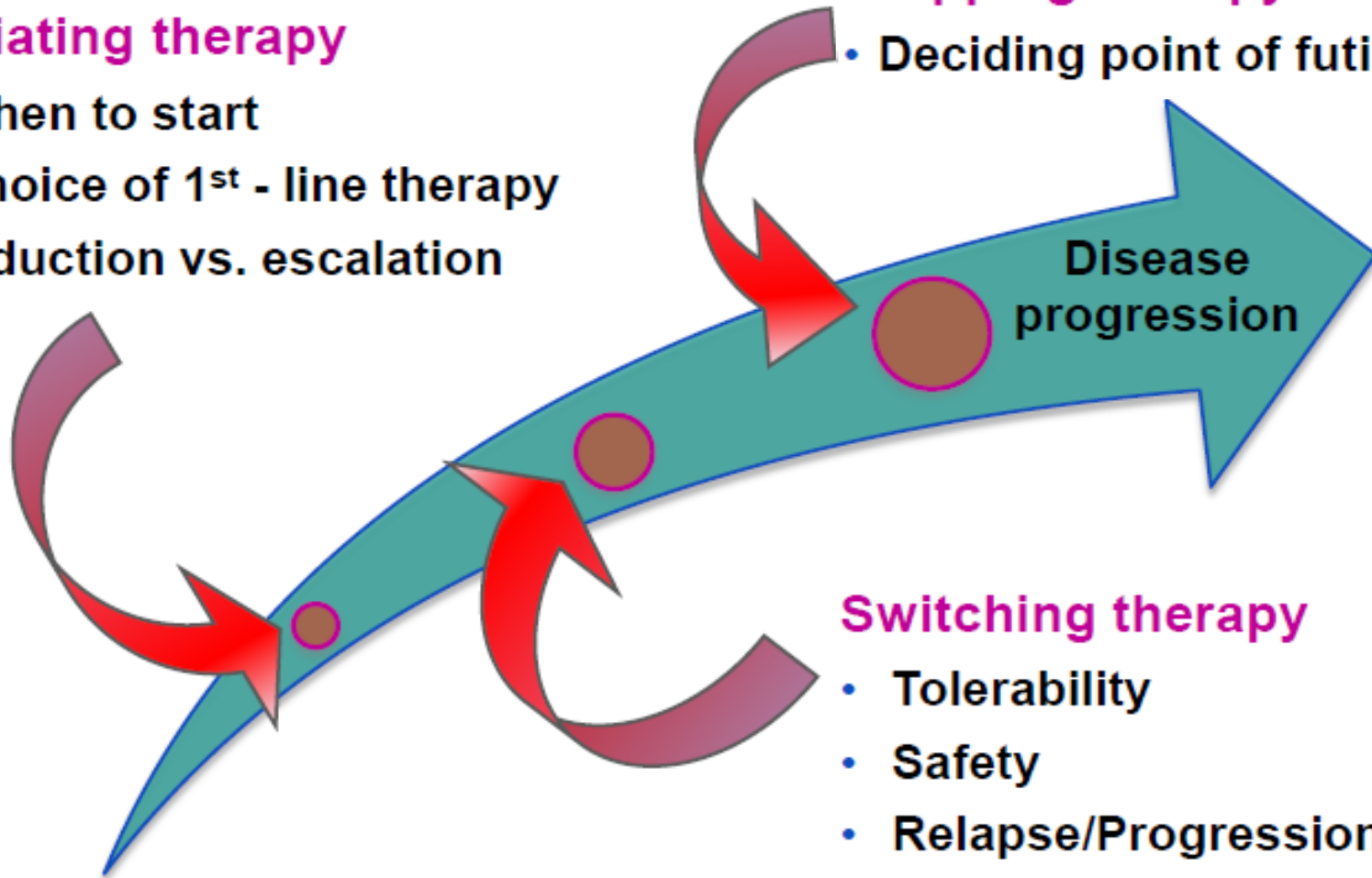
- When to start
- Choice of 1st - line therapy
- Induction vs. escalation

Stopping therapy

- Deciding point of futility

Switching therapy

- Tolerability
- Safety
- Relapse/Progression/MRI



When to stop?



Stable



SPMS

When to stop?

The researchers suggest that a conversation about discontinuing DMT could be "reasonable" for the following patient subsets:

1. Patients with **SPMS** who have ongoing progression and **no new brain or spinal cord MRI lesions** in the **prior 12 to 24 months**.
2. **Stable RRMS patients, aged 65 or older, with no brain or spinal cord lesion during the prior 5 years.**
3. Patients who are **pregnant, trying to conceive, or breastfeeding** (because of safety concerns).

Practice guideline recommendations summary: Disease-modifying therapies for adults with multiple sclerosis

Report of the Guideline Development, Dissemination, and Implementation
Subcommittee of the American Academy of Neurology

Statement 2a

Clinicians should assess the likelihood of future relapse in individuals with SPMS by assessing patient age, disease duration, relapse history, and MRI-detected activity (e.g., frequency, severity, time since most recent relapse or gadolinium-enhanced lesion) (Level B).

Statement 2b

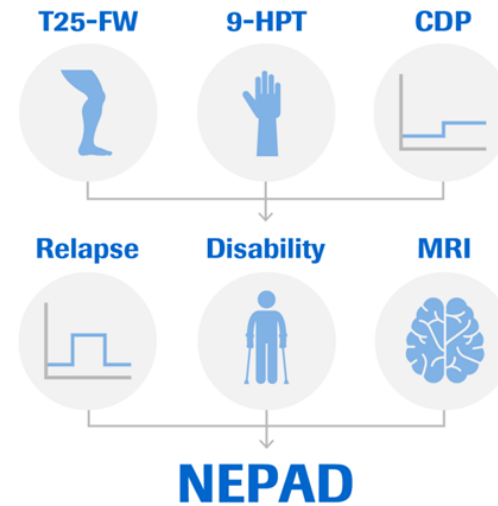
Clinicians may advise discontinuation of DMT in people with SPMS who do not have ongoing relapses (or gadolinium-enhanced lesions on MRI activity) and have not been ambulatory (EDSS 7 or greater) for at least 2 years (Level C).

Reassess

Wait a minute.....



<p>Primary progressive (progressive accumulation of disability from onset)</p> <p>↑</p> <p>Progressive disease</p> <p>↓</p> <p>Secondary progressive (progressive accumulation of disability after an initial relapsing course)</p>	Active ^a and with progression ^b
	Active ^a but without progression
	Not active but with progression ^b
	Not active and without progression (stable disease)



No Evidence of Progression or Active Disease

When to stop?

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Discontinuation of Disease Modifying Therapies (DMTs) in Multiple Sclerosis (MS) (DISCOMS)



The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing a study does not mean it has been evaluated by the U.S. Federal Government. [Know the risks and potential benefits](#) of clinical studies and talk to your health care provider before participating. Read our [disclaimer](#) for details.

ClinicalTrials.gov Identifier: NCT03073603

[Recruitment Status](#) ⓘ : Recruiting

[First Posted](#) ⓘ : March 8, 2017

[Last Update Posted](#) ⓘ : January 8, 2018

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Key decision making points in Treatment of MS

Initiating therapy

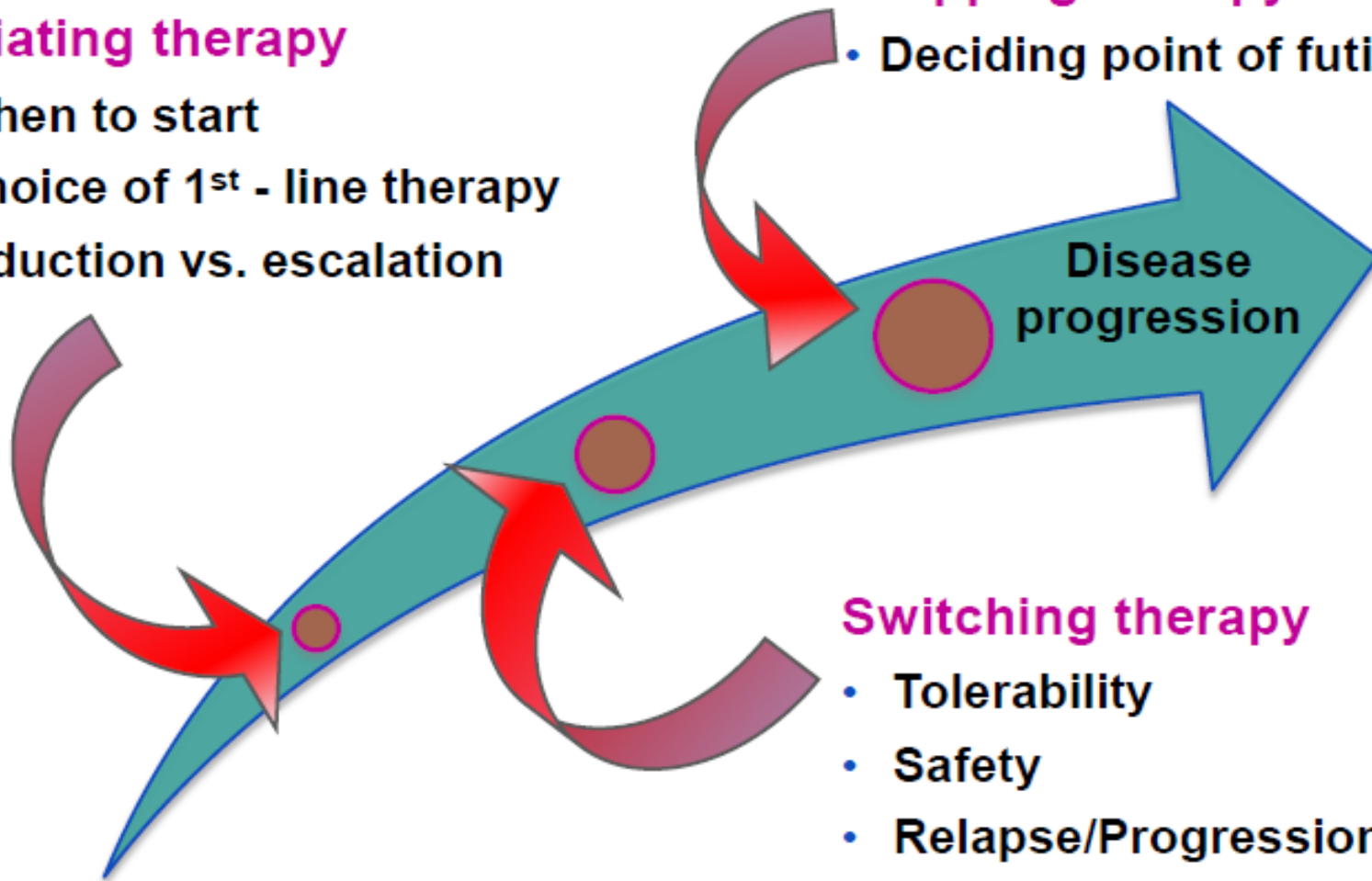
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Navigating the multiple facets of management of MS





THANK YOU

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