From MAR to SMART: Advanced Methods for Integrating Patient Preferences in Regulatory Science

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What are Patient Preferences?

Formally

Qualitative or quantitative assessments of the relative desirability or acceptability to patients of specified alternatives or choices among outcomes or other attributes that differ among alternative health interventions*

More simply, preferences assess

Type	What it Measures
Attributes	What matters
Relative Importance	How much it matters
Tradeoffs	What tradeoffs patients are willing to make between benefits, harms, and other characteristics of treatment

Willingness to pay, Maximum acceptable risk, Minimal required benefit →

Rigor & complexity ↓

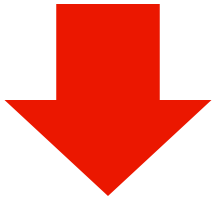
*https://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm446680.pdf

Adapted from RTI-HS and MDIC

What is a MAR/MAB?

Maximum acceptable risk (MAR): The maximum level of risk that people are willing to accept in exchange for a given increase in benefit

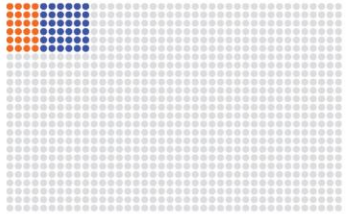
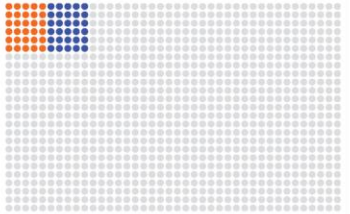
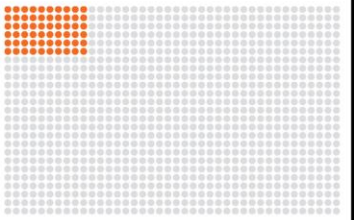
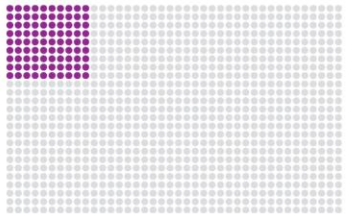
Minimum required/acceptable benefit (MAB): The minimum level of benefit that people are willing to accept in exchange for a given increase in risk



These measures can support target product profile development, endpoint selection, benefit-risk assessment, and regulatory approval

Example – Preferences for lung cancer interception therapy

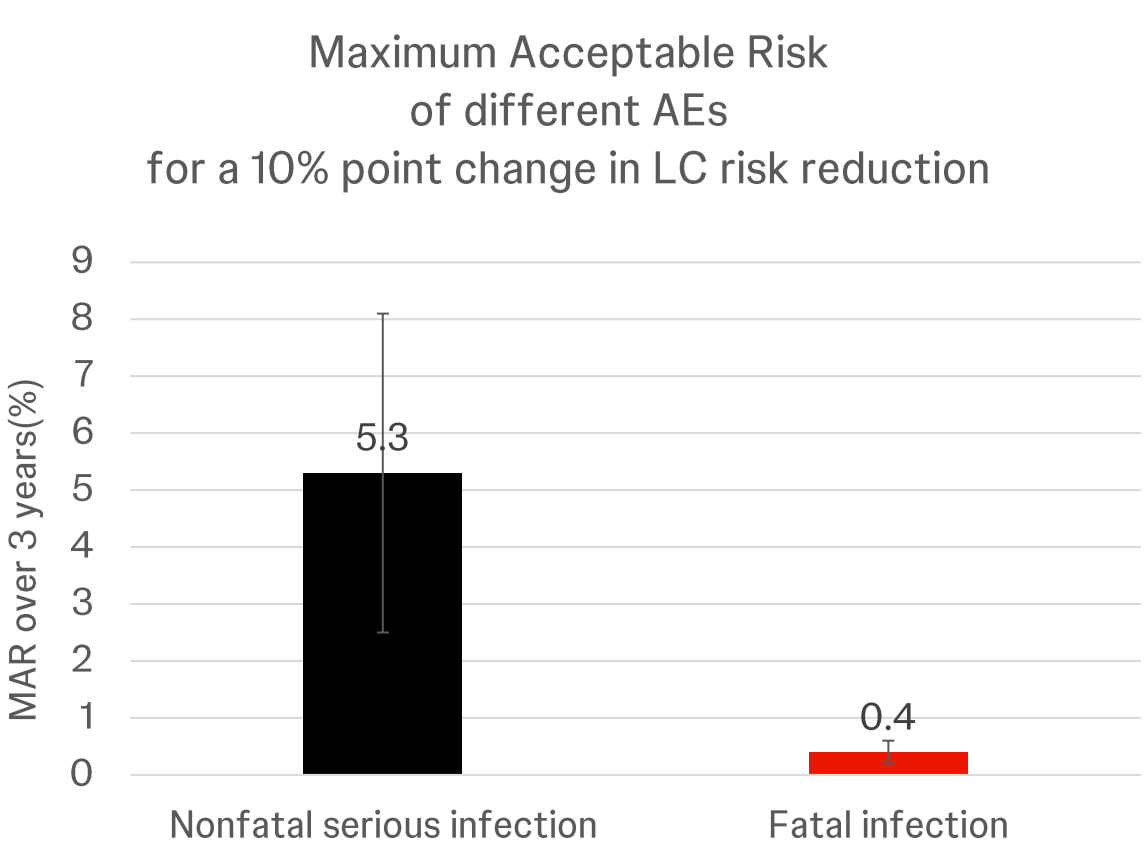
This example uses a baseline risk of lung cancer of 6%

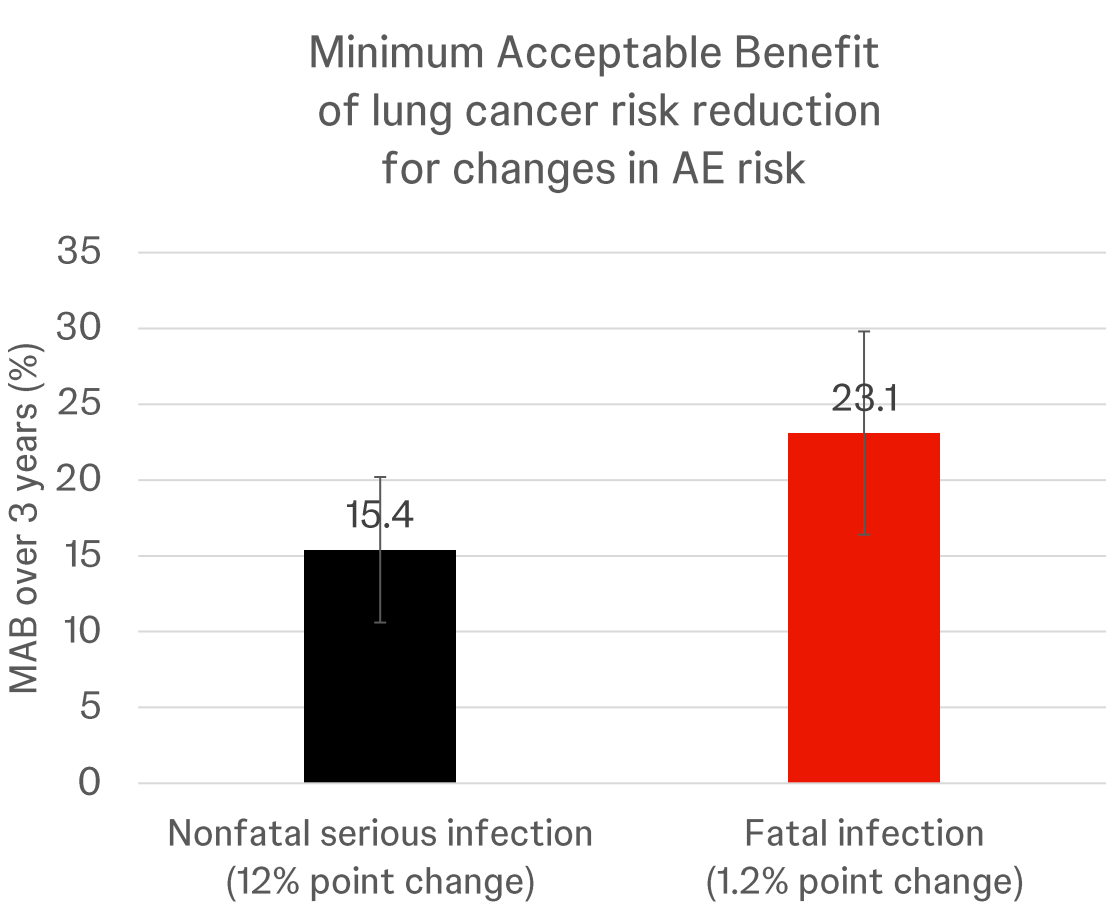
Feature (Attribute)	Medication A	Medication B	No Treatment
Risk of lung cancer over 3 years	 Risk is 2.4% (24 out of 1,000) Prevents 36 cases	 Risk is 3% (30 out of 1,000) Prevents 30 cases	 Risk is 6% (60 out of 1,000)
Severity of injection site reaction	Moderate	None	None
Risk of nonfatal serious infection over 3 years	 9% (90 out of 1,000)	 3% (30 out of 1,000)	0% (0 out of 1,000)
Risk of death from serious infection over 3 years	0.3% (3 out of 1,000)	 1.5% (15 out of 1,000)	0% (0 out of 1,000)
Which option would you choose?			

SOURCE: Janssen et al., Patient Preferences for Lung Cancer Interception Therapy. JAMA Netw Open. 2023 Nov. PMCID: PMC10638649.

MARs and MABs for Lung Cancer Risk Reductions

Two sides of the same coin





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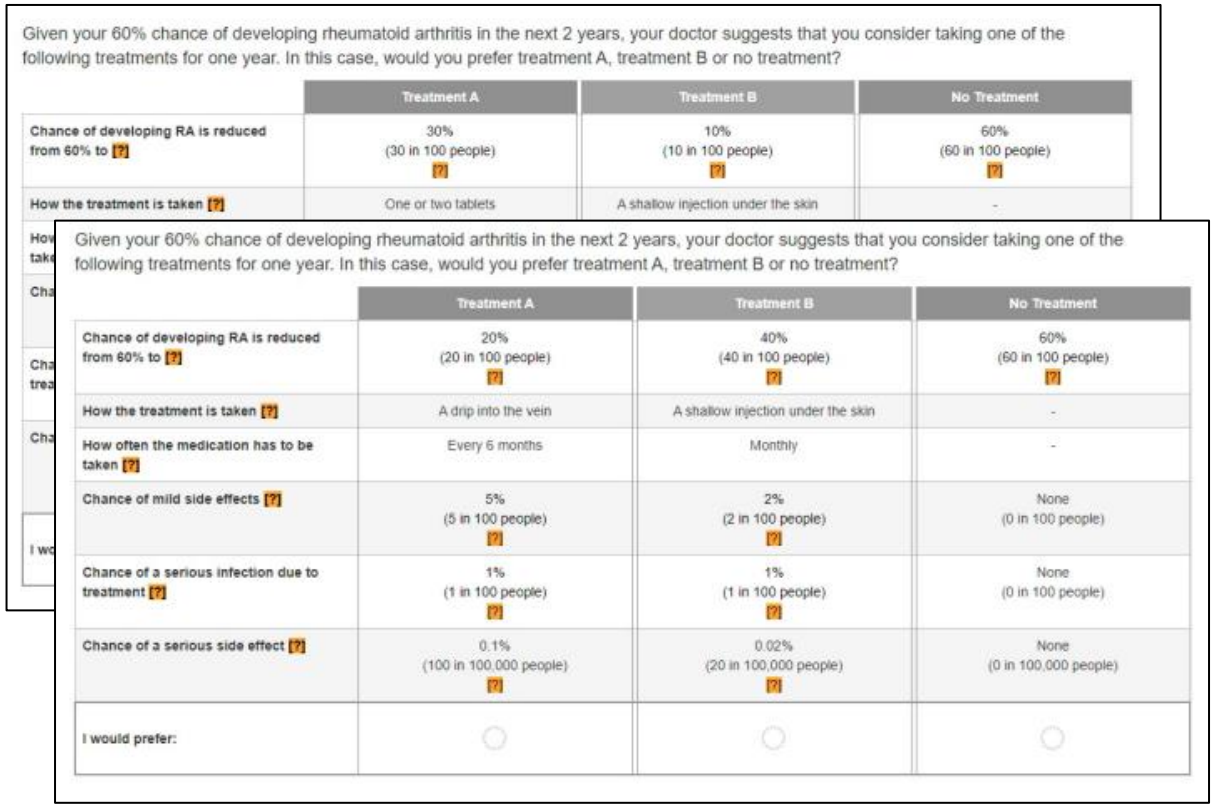
SOURCE: Janssen et al., Patient Preferences for Lung Cancer Interception Therapy. JAMA Netw Open. 2023 Nov. PMCID: PMC10638649.

How to measure MAR

Discrete-Choice Experiment: indirect elicitation of MAR



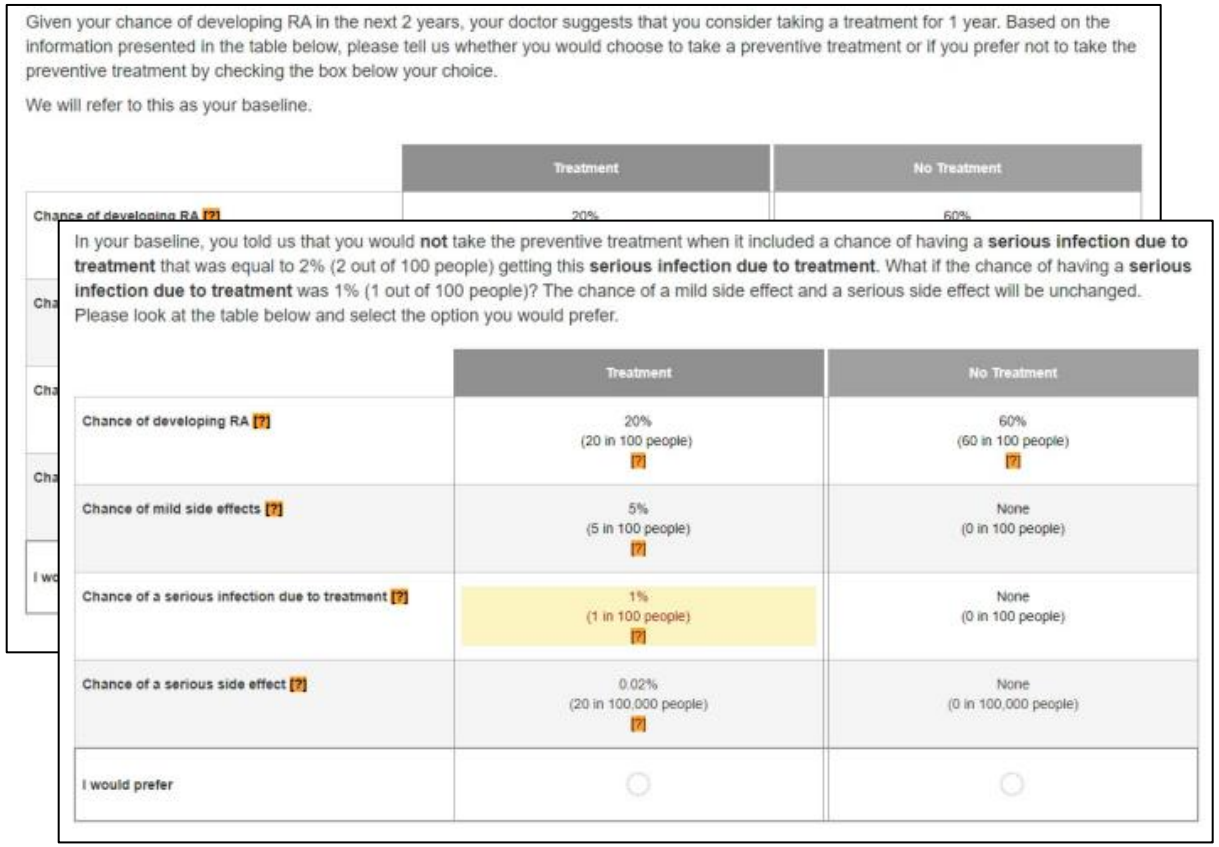
Given your 60% chance of developing rheumatoid arthritis in the next 2 years, your doctor suggests that you consider taking one of the following treatments for one year. In this case, would you prefer treatment A, treatment B or no treatment?

	Treatment A	Treatment B	No Treatment
Chance of developing RA is reduced from 60% to [?]	30% (30 in 100 people) [?]	10% (10 in 100 people) [?]	60% (60 in 100 people) [?]
How the treatment is taken [?]	One or two tablets	A shallow injection under the skin	-

Given your 60% chance of developing rheumatoid arthritis in the next 2 years, your doctor suggests that you consider taking one of the following treatments for one year. In this case, would you prefer treatment A, treatment B or no treatment?

	Treatment A	Treatment B	No Treatment
Chance of developing RA is reduced from 60% to [?]	20% (20 in 100 people) [?]	40% (40 in 100 people) [?]	60% (60 in 100 people) [?]
How the treatment is taken [?]	A drip into the vein	A shallow injection under the skin	-
How often the medication has to be taken [?]	Every 6 months	Monthly	-
Chance of mild side effects [?]	5% (5 in 100 people) [?]	2% (2 in 100 people) [?]	None (0 in 100 people)
Chance of a serious infection due to treatment [?]	1% (1 in 100 people) [?]	1% (1 in 100 people) [?]	None (0 in 100 people)
Chance of a serious side effect [?]	0.1% (100 in 100,000 people) [?]	0.02% (20 in 100,000 people) [?]	None (0 in 100,000 people)
I would prefer:	○	○	○

Threshold Techniques: Direct elicitation of MAR



Given your chance of developing RA in the next 2 years, your doctor suggests that you consider taking a treatment for 1 year. Based on the information presented in the table below, please tell us whether you would choose to take a preventive treatment or if you prefer not to take the preventive treatment by checking the box below your choice.

We will refer to this as your baseline.

	Treatment	No Treatment
Chance of developing RA [?]	20%	60%

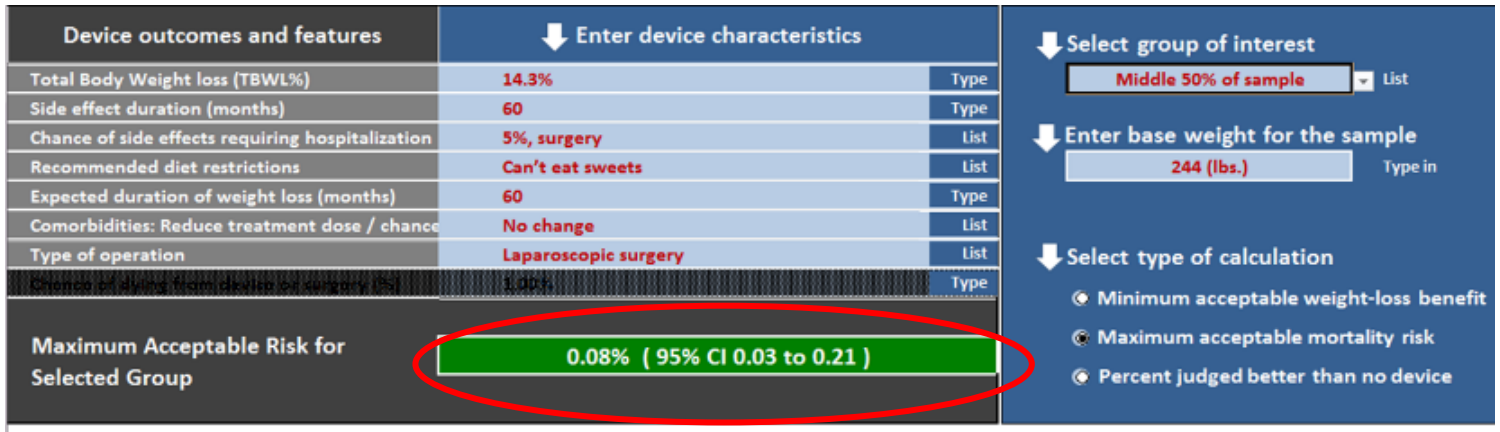
In your baseline, you told us that you would **not** take the preventive treatment when it included a chance of having a **serious infection due to treatment** that was equal to 2% (2 out of 100 people) getting this **serious infection due to treatment**. What if the chance of having a **serious infection due to treatment** was 1% (1 out of 100 people)? The chance of a mild side effect and a serious side effect will be unchanged. Please look at the table below and select the option you would prefer.

	Treatment	No Treatment
Chance of developing RA [?]	20% (20 in 100 people) [?]	60% (60 in 100 people) [?]
Chance of mild side effects [?]	5% (5 in 100 people) [?]	None (0 in 100 people)
Chance of a serious infection due to treatment [?]	1% (1 in 100 people) [?]	None (0 in 100 people)
Chance of a serious side effect [?]	0.02% (20 in 100,000 people) [?]	None (0 in 100,000 people)
I would prefer	○	○

J&J Source: Veldwijk et al.,. Maximum Acceptable Risk Estimation Based on a Discrete Choice Experiment and a Probabilistic Threshold Technique. Patient. 2023 Nov; : PMC10570171.

MAR and health authority decisions: FDA weight loss device

FDA co-developed a stated-preference survey to elicit benefit-risk preferences for multiple attributes of hypothetical obesity devices



FDA Weighs Patients' Risk Tolerance in Approving Obesity Device

This article was originally published in The Pink Sheet Daily

20 Jan 2015 | **NEWS**

Source: Ho MP, Gonzalez JM, Lerner HP, Neuland CY, Whang JM, McMurry-Heath M, Hauber AB, Irony T. Incorporating patient-preference evidence into regulatory decision making. Surg Endosc. 2015 Oct;29(10):2984-93. doi: 10.1007/s00464-014-4044-2. Epub 2015 Jan 1. PMID: 25552232.

MAR and Health Authority Decisions: EMA Alopecia

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

20 July 2023
EMA/357337/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Litfulo

International non-proprietary name: ritlecitinib

Pro

Table 21: Maximum acceptable risks (MAR) in exchange for a 20% increase in the probability of SALT≤20

3-Year Risk	Overall Sample	US Sample
Serious Infection	7.40 [5.47; 9.33]	3.71 [2.62; 4.79]
Cancer (including NMSC)	2.50 [1.87; 3.14]	2.12 [1.19; 3.05]
Blood Clot	9.34 [6.42; 12.26]	5.65 [3.43; 7.87]

The MAR for a given 3-year risk is the percentage-point increase in the individual risk that will yield a utility loss that will exactly offset the utility gain from a 20 percentage-point increase in the probability of achieving SALT≤20 from the patient perspective.

Based on the patient preference studies in adults and adolescents, it is estimated that a small majority of the 'average' patient with AA can be expected to prefer ritlecitinib 50 mg over no treatment when making an informed choice.

The CHMP concluded that the efficacy data supports the following indication: 'Litfulo is indicated for the treatment of severe alopecia areata in adults and adolescents 12 years of age and older (see section 5.1)'.

J&J Litfulo : EPAR - Public Assessment Report. https://www.ema.europa.eu/en/documents/assessment-report/litfulo-epar-public-assessment-report_en.pdf

Complications in estimating MARs/MABs

This example uses a baseline risk of lung cancer of 6%

Baseline risk can impact MAR/MAB

Risk framing can impact MAR/MAB

Continuous/categorical specification of risk affects MAR estimates

Most MAR/MABs are calculated for individual risks, most Tx options have more than one risk

Including an opt-out option/how the opt-out is modeled can impact MAR/MAB

Feature (Attribute)	Medication A	Medication B	No Treatment
Risk of lung cancer over 3 years	Risk is 2.4% (24 out of 1,000) Prevents 36 cases	Risk is 3% (30 out of 1,000) Prevents 30 cases	Risk is 6% (60 out of 1,000)
Severity of injection site reaction	Moderate	None	None
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Introducing the panel

Ellen Janssen, PhD

Director, Benefit-Risk/Epidemiology, Johnson & Johson

Marco Boeri, PhD

Director of Preference Research, Open Health

Juan Marcos González Sepúlveda, PhD

Associate Professor, Duke University School of Medicine

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Download the tool

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