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HTA Assessments for Multi-Purpose Contrast Agents: Insights and Solutions to Formal HTA Challenges

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The opportunity

Innovative MRI contrast agents have been developed to minimize patient exposure to gadolinium by ≥50% without compromising imaging outcomes.

- This marks a major mile-stone after nearly 2 decades without new multi-purpose contrast agents for MRI.
- Hundreds of millions have been invested in full clinical programs to minimize patients' exposure to Gd.[1]
- 65 million contrast enhanced MRI are conducted globally each year.
- A reduction of at least 50% Gd is a ground-breaking innovation for CE-MRI.[2]

Development was founded on the need to more closely meet the ALARA principle (As Low As Reasonably Achievable).

Medical recommendations

- ALARA is a longstanding policy goal to minimize exposure to necessary imaging technologies (radiation, contrast agents).
- Gd is an essential component of MRI contrast agents. Aligning with ALARA was limited due to the lower relaxivity of SoC MRI contrast agents.
- US and EU medical guidelines provide clear recommendations: *"…the lowest dose needed for diagnosis should be used as deemed necessary by the supervising radiologist"*[3] and *"…use the smallest amount of contrast medium necessary for a diagnostic result."*[4]

Regulatory recommendations

- EMA suspended marketing authorization of multipurpose linear GBCAs and recommended macrocyclic GBCAs be used at *"the lowest dose that enhances images sufficiently to make diagnoses and only when unenhanced scans are not suitable."*[5]
- The FDA mandated that all GBCA labels update the text surrounding Gd retention.[6]

While ALARA is a stated medical and policy goal, in many countries, it is neither recognized as a decision parameter nor incentivized within pricing and reimbursement decision-making processes.

Multi-purpose contrast agents (diagnostics) are unlikely to meet HTA evidence requirements for pharmaceutical treatments.[7,8]

HTA often considers contrast agents in isolation from highly interconnected sub-national pricing and reimbursement (P&R) processes.

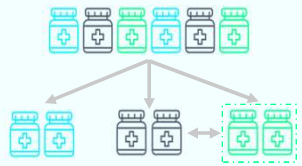
Very few formal health technology assessments of contrast agents have taken place in the past, so this challenge has not received attention.

Incentives need to be built into access decision-making processes if ALARA is to be achieved for a broad range of patients.

How to realize the opportunity

A framework should be established for contrast agent categorization that enables meaningful differentiation between (and competition within) classes.

Methodological solution



1. National authorities should define criteria that recognize the value of reduced doses for all patients and group similar products (e.g., generations of MRI contrast agents by Gd dose).
2. Differentiate between classes in national HTA and sub-national tender specifications to align with policy objectives (e.g., ALARA).
3. Foster competition within classes while allowing for differentiated recognition of value between classes (e.g., in- vs. outpatient, patient cases).

- A classification system is not a concern for the public health systems, as contrast agents are reimbursed as part of the procedure, not separately.

Best practice example

Italy classifies MRI contrast agents via a sub-national tender system.

- Every API receives an own lot in the tender.
- A winner is determined in each class, promoting intra-class and inter-class competition.
- Radiologists have access to the best product per class.[a]

By fostering competition between manufacturers at the sub-national level, innovation towards "ever-lower ALARA" will be incentivized without additional spend to the overall healthcare system.

Patient access to new and Gd-reduced contrast agents may be accelerated.

Investment in future contrast media innovation is incentivized.

Competition between manufacturers with similar Gd doses will foster a focus on cost-benefit ratios.

Elucirem/Vueway HTA case studies:

France: ASMR rating V (''no clinical added value'') is accompanied by written recognition by HAS mentioning in the ''Place of the therapeutic strategy'' section *"…the potential benefits of Gd reduction to patients with the introduction of low Gd-dose MRI contrast agents"*.[8]

Germany: *"An additional benefit is not proven,"* and Germany is yet to adopt similar measures to recognize or incentivize ALARA in its evaluations of multipurpose contrast agents in the AMNOG process.

Methods

This study first analyzed the national HTA assessments in Germany and France for the two most recently approved MRI contrast agents, Elucirem and Vueway (INN gadopiclenol), focusing on:

1. Regulatory requirements
2. HTA evidence criteria

These findings were compared to alternative evidence options available to manufacturers.

Then, we examined the sub-national P&R steps toward the commercialization of these products, drawing conclusions on how various stakeholders can reconcile the conflict between evidence requirements and feasible evidence options. Italy's sub-national P&R processes have been identified as best-in-class.

This dual approach—fact-based analysis, then a systematic review—facilitates practical recommendations for future benefit assessments of contrast agents, extending beyond formal national HTA to include sub-national P&R evaluations.

Notes: a) In this context, the "best" product refers to the one that offers the highest cost-benefit rating.

Abbreviations: ALARA, as low as reasonably achievable; AMNOG, Arzneimittelmarktneuordnungsgesetz; API, Active Pharmaceutical Ingredient; ASMR, amélioration du service médical rendu; CE-MRI, contrast-enhanced magnetic resonance imaging; EMA, European Medicines Agency; EU, European Union; FDA, Food and Drug Administration; GBCA, gadolinium-based contrast agent; Gd, gadolinium; HTA, health technology assessment; INN, International Non-proprietary Name; MRI, magnetic resonance imaging; P&R, pricing and reimbursement; SoC, standard of care; US, United States.

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