Appendices for Safe Use of Contrast Media Part 2

This part comprises:

1. **Hypersensitivity reactions after contrast media administration**
2. **Safe use of gadolinium-containing contrast media**
3. **Safe injection of contrast media through central catheters and ports**
4. **Contrast media extravasation**

INITIATED BY
Radiological Society of the Netherlands

IN ASSOCIATION WITH
Netherlands Association of Internal Medicine
Dutch Federation for Nephrology
Netherlands Society of Intensive Care
Dutch Association of Hospital Pharmacists
Association of Surgeons of the Netherlands
The Netherlands Society of Cardiology
Netherlands Society of Emergency Physicians
The Dutch Society of Allergology and Clinical Immunology
Dutch Society of Dermatology and Venereology

WITH THE ASSISTANCE OF
Knowledge Institute of Medical Specialists

FINANCED BY
Quality Funds of Medical Specialists

Colophon

RICHTLIJN SAFE USE OF CONTRAST MEDIA - PART 2

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Appendices to module 1

Knowledge Gaps

It is unclear which treatments of acute hypersensitivity reactions after CM administration lead to a higher severity of complaints. The following outcomes would be relevant to study: duration of acute reaction, morbidity, mortality, costs, hospitalization in an IC-unit, length of stay.

Quality Assurance Indicators

Every hospital needs a local protocol for management of acute hypersensitivity reactions after CM administration, accessible in all rooms where CM are administered.

1. Hospital-wide protocols for management of acute hypersensitivity reactions after CM administration, accessible in all rooms where CM are administered	
Operationalization	Is there an overall hospital-wide protocol or process-agreement for management of acute hypersensitivity reactions after CM administration? And is this protocol accessible in all rooms where CM is administered?
Numerator	Not applicable
Denominator	Not applicable
Type of indicator	Input
In- and exclusion criteria	Inclusion A hospital-wide protocol for management of acute hypersensitivity reactions after CM administration. This protocol is accessible in all rooms where CM is administered.
Quality domain	Safety and effectivity
Measuring frequency	Once a year
Report year	2020
Frequency of report	Once a year

Medication for treatment of acute reactions after CM administration should be available in every room where CM is administered.

2. Hospital-wide protocols about prevention of PC-AKI	
Operationalization	Is there medication for treatment of acute reactions after CM administration available in every room where CM is administered?
Numerator	Not applicable
Denominator	Not applicable
Type of indicator	Input
In- and exclusion criteria	Inclusion Medication for treatment of acute reactions after CM administration available in every room where CM is administered. As a minimum the following medication should be available: adrenaline, salbutamol, H1-antihistamine (clemastine) IV, corticosteroid IV.
Quality domain	Safety and effectivity
Measuring	Once a year

frequency	
Report year	2020
Frequency of report	Once a year

Implementation of Recommendations

Recommendation	Time frame for implementation: <1 year, 1 to 3years or >3 years	Expected effect on costs	Limitations for implementation	Barriers to implementation[1]	Actions needed for implementation[2]	Parties responsible for actions[3]	Other remarks
Preparation: • Have the drugs (as a minimum requirement: adrenaline, salbutamol, H1-antihistamine (clemastine) IV, and corticosteroid IV (e.g. prednisolone)), equipment and protocol for treatment of an acute adverse reaction readily available in every room where contrast agents are administered. • Adhere to local protocols for accessibility of a resuscitation and emergency response team. • Keep every patient with an acute hypersensitivity reaction to CM in a medical environment for at least 30 minutes after contrast agent injection. Moderate and severe reactions need a prolonged observation.	1 to 3 years	None	Lack of knowledge, lack of availability of drugs for treatment of acute reactions in rooms where CM is administered	Lack of knowledge, lack of availability of drugs for treatment of acute reactions in rooms where CM is administered	Dissemination of guideline, development of local protocols for treatment of acute hypersensitivity reactions after CM	NVvR, NVVC	
Acute management general principles: • Check and stabilize patient according to the ABCDE method • Stop infusing contrast agent and replace IV line with crystalloid. • Dyspnoea or stridor: let patient sit up • Hypotension: keep patient in prone position, raise legs • Consider measuring serum tryptase (see recommendations in chapter Laboratory Diagnosis of Hypersensitivity Reactions to Contrast Media)	1 to 3 years	None	Lack of knowledge, lack of availability of drugs for treatment of acute reactions in rooms where CM is administered	Lack of knowledge, lack of availability of drugs for treatment of acute reactions in rooms where CM is administered	Spreading knowledge of guideline, development of local protocols for treatment of acute hypersensitivity reactions after CM	NVvR, NVVC	

• Record acute allergic reactions in allergy registry (see chapter Organization of Healthcare) • *Note: After administration of clemastine the patient may no longer be able (or insured) to drive a car/motorcycle or to operate machinery.*							
Severe reactions: **Cardiac or respiratory arrest:** • Start CPR • Call the CPR team. **Anaphylactic reaction or stridor:** • Call rapid response team (SIT-team) • Give oxygen 10-15L/min with non-rebreathing mask • Give 0.5mg adrenaline IM in lateral upper thigh • Give fluid bolus of crystalloid 500ml IV in 10 minutes, repeat as necessary. • Consider nebulizing with salbutamol 5mg or budesonide 2mg for stridor • Give clemastine 2mg IV • Consider adding corticosteroid (e.g. prednisolone 50mg iv, *)	1 to 3 years	None	Lack of knowledge, lack of availability of drugs for treatment of acute reactions in rooms where CM is administered	Lack of knowledge, lack of availability of drugs for treatment of acute reactions in rooms where CM is administered	Spreading knowledge of guideline, development of local protocols for treatment of acute hypersensitivity reactions after CM	NVvR, NVVC	
Moderate reactions: Consider transferring the patient to a department with facilities for monitoring of vital functions. **Isolated bronchospasm:** • Salbutamol 2.5-5mg nebulization in oxygen by facemask 10-15 L/min (nebulization is easier to administer and more effective than dose aerosol). • In mild cases asthma patients may use their own salbutamol dose aerosol. • In case of deterioration give adrenaline 0.5mg IM and consider call rapid response team **Isolated facial oedema without stridor:** • Give oxygen 10-15L/min via anon-	1 to 3 years	None	Lack of knowledge, lack of availability of drugs for treatment of acute reactions in rooms where CM is administered	Lack of knowledge, lack of availability of drugs for treatment of acute reactions in rooms where CM is administered	Spreading knowledge of guideline, development of local protocols for treatment of acute hypersensitivity reactions after CM	NVvR, NVVC	

rebreathing mask • Give clemastine 2mg IV • If oedema is severe or near airways or if stridor develops: treat as anaphylaxis **Isolated urticaria/diffuse erythema:** • Give clemastine 2mg IV • If accompanied by hypotension: treat as anaphylaxis **Isolated hypotension:** • Give bolus of crystalloid 500ml IV, repeat as necessary. • If accompanied by bradycardia, consider atropine 0.5mg IV • If accompanied by other symptoms: treat as anaphylaxis							
Mild reactions: **General:** • Mild reactions may only need reassurance • Observe vital signs until symptoms resolve • Do not remove iv access during observation **Consider:** • Prescribing a non-sedating antihistamine, e.g. desloratadine 5mg PO (once daily) for mild allergic reactions • Ondansetron 4mg IV for protracted vomiting	1 to 3 years	None	Lack of knowledge, lack of availability of drugs for treatment of acute reactions in rooms where CM is administered	Lack of knowledge, lack of availability of drugs for treatment of acute reactions in rooms where CM is administered	Spreading knowledge of guideline, development of local protocols for treatment of acute hypersensitivity reactions after CM	NVvR, NVVC	

[1] Barriers can be found at multiple levels. They can exist at the level of the consultant, the hospital organisation, and the health care system.

[2] Actions needed for implementation, but also actions to promote implementation. Think about checks during quality visits, guideline publication, information of hospital management, et cetera.

[3] Who is responsible for implementation of recommendations will largely be determined by the level where the barriers are expected to be.

Evidence Tables

Not applicable.

Exclusion Table

After full text review

Author and year	Reasons for exclusion
Boyd, 2017	Narrative review. No control arm
Brockow, 2011 20	Narrative review. No control arm
Bush, 1991	Patient group not treated with CM. Does not cover treatment
Cochran, 2005	Expert opinion
Cohan, 1996	Narrative review.
Collins, 2009	Narrative review. No control arm.
Coors, 2006	Narrative review. No control arm.
Davis, 2015	Narrative review. No control arm
Dawson, 2002	Narrative review. No control arm. Does not cover treatment
Drain, 2001	Narrative review. No control arm.
Hash, 1999	Narrative review. No control arm
Hollingswerth, 1991	Patient group not treated with CM
Iyer, 2013	Narrative review. No control arm.
Kounis, 2015	Narrative review. No control arm
Liebhart, 2007	Narrative review. No control arm. Patient group not treated with CM
Marycz, 2014	Narrative review. No control arm
Masch, 2016	Narrative review. No control arm
Meth, 2006	Narrative review. No control arm.
Morcos, 2001	Narrative review. No control arm.
Morcos, 2005	Expert opinion
Morcos, 2005	Narrative review. No control arm.
Morcos, 2006	Narrative review. No control arm.
Morzycki, 2017	Narrative review. No control arm
Namasivayam, 2006a	Narrative review. No control arm. Patient group not treated with CM
Namasivayam, 2006b	Narrative review. No control arm.
Nandwana, 2015	Narrative review. No control arm. Patient group not treated with CM
Nayak, 2009	Narrative review. No control arm.
Newmark, 2012	Narrative review. No control arm
Petscavage, 2012	Patient group not treated with CM
Pumphrey, 2004	Narrative review. No control arm.
Ring, 2010	Narrative review. Patient group not treated with CM
Rose, 2015	Narrative review
Sadler, 1994	Patient group not treated with CM
Seikh, 2013	Expert opinion. Patient group not treated with CM
Shellock, 1993	Patient group not treated with CM
Skowronski, 1987	Patient group not treated with CM
Szebeni, 2004	Narrative review. No control arm.
Thompsen 1998b	Narrative review. No control arm.
Thompsen, 1998a	Narrative review. No control arm.
Thompsen, 2004	More recent guideline available
Thompsen, 2016	Narrative review. No control arm
Toncic, 2009	Narrative review. No control arm. Patient group not treated with CM
Toogood, 1987	Patient group not treated with CM
Wang, 2008	Narrative review. No control arm.
Wang, 2014	No comparison between effectivity of several treatments
Winbery, 2002	Narrative review. No control arm.
Wolkenstein, 1995	Narrative review. No control arm. Patient group not treated with CM

Literature Search

Database	Search String	Total
PubMed 1985 –	("Contrast Media"[Mesh] OR contrast medi* [tiab] OR contrast agent* [tiab] OR contrast material* [tiab] OR contrast dose [tiab] OR contrast doses [tiab] OR contrast dosage [tiab] OR radiocontrast medi* [tiab] OR radiocontrast agent* [tiab] OR radiopaque medi* [tiab] OR radiocontrast dose [tiab] OR radiocontrast doses [tiab] OR radiocontrast dosage [tiab] OR "Barium"[Mesh] OR barium [tiab]	328

december 2017	OR gadolinium [tiab] OR microbubble* [tiab]) AND (("Drug Hypersensitivity"[Mesh] OR hypersensitiv* [tiab] OR allergic* [tiab] OR anaphylaxis [tiab] OR anaphylact* [tiab] OR adverse reaction*[tiab] OR urticaria* [tiab] OR diffuse erythema [tiab] OR facial edema [tiab] OR angioedema [tiab] OR bronchospasm* [tiab] OR laryngeal edema [tiab] OR anaphylactic shock [tiab] OR hypotension [tiab] OR pulmonary edema [tiab] OR cardiac arrest [tiab] OR respiratory arrest [tiab]) AND (acute [tiab] OR after administration [tiab] OR rapid* [tiab] OR severe [tiab])) AND (treatment [tiab] OR treat [tiab] OR recommend* [tiab]) AND ("english"[Language]) AND ("1985"[Date - Publication] : "3000"[Date - Publication]) = 215	
Embase (Elsevier)	contrast medium'/exp/mj OR (((contrast OR radiocontrast) NEAR/2 (medi* OR agent* OR material* OR dose OR doses OR dosage)):ab,ti) OR 'radiopaque medi*':ab,ti OR 'barium'/exp/mj OR barium:ab,ti OR 'gadolinium'/exp/mj OR gadolinium:ab,ti OR 'microbubble'/exp/mj OR microbubble*:ab,ti) AND (('hypersensitivity'/exp OR hypersensitiv*:ab,ti OR allergic*:ab,ti OR anaphylaxis:ab,ti OR anaphylactic:ab,ti OR 'adverse reaction*':ab,ti OR urticaria*:ab,ti OR 'diffuse erythema':ab,ti OR 'facial edema':ab,ti OR angioedema:ab,ti OR bronchospasm:ab,ti OR 'laryngeal edema':ab,ti OR 'anaphylactic shock':ab,ti OR hypotension:ab,ti OR 'pulmonary edema':ab,ti OR 'cardiac arrest':ab,ti OR 'respiratory arrest':ab,ti) AND (acute:ab,ti OR 'after administration':ab,ti OR rapid*:ab,ti OR severe:ab,ti)) AND (treatment:ab,ti OR treat:ab,ti OR recommend*:ab,ti)) AND [english]/lim AND [1985-2018]/py NOT 'conference abstract':it NOT (('animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp) = 282 (279 unique)	

Appendices to module 2

Knowledge Gaps
It is unclear whether any treatment of late hyper sensitivity reactions after contrast administration leads to a quicker recovery, a less serious course, sequelae, mortality, morbidity hospitalization. It is also not clear whether one treatment options might lead to a better outcome (as described in the previous sentence) compared to another.

Quality Assurance Indicators
None.

Implementation of Recommendations

Recommendation	Time frame for implementation: <1 year, 1 to 3years or >3 years	Expected effect on costs	Limitations for implementation	Barriers to implementation[1]	Actions needed for implementation[2]	Parties responsible for actions[3]	Other remarks
Warn patients who have had a previous hypersensitivity reaction to contrast media, that a late hypersensitivity reaction may be possible, usually a skin reaction.	1 to 3 years	None	Lack of knowledge of guideline. Lack of experience for recognizing late hypersensitivity reactions after contrast administrations.	Lack of knowledge of guideline.	Disseminations of guideline	NVvR	
Patients should contact their general practitioner if they have a late hypersensitivity reaction after CM administration. Consider informing the radiology department about the occurrence and symptoms of a late hypersensitivity reaction after CM administration.	1 to 3 years	None	Lack of knowledge of guideline. Lack of experience for recognizing late hypersensitivity reactions after contrast administrations.	Lack of knowledge of guideline.	Disseminations of guideline	NVvR	
When the symptoms of a late hypersensitivity reaction are mild, a wait-and-see approach can be justified.	1 to 3 years	None	Lack of knowledge of guideline. Lack of experience for recognizing late hypersensitivity reactions after contrast administrations.	Lack of knowledge of guideline.	Disseminations of guideline	NVvR	
Treat late hypersensitivity reactions symptomatically. Consider treatment of skin reactions with oral or topical corticosteroids.	1 to 3 years	None	Lack of knowledge of guideline. Lack of experience for recognizing late hypersensitivity reactions after contrast administrations.	Lack of knowledge of guideline.	Disseminations of guideline	NVvR	
When severe symptoms develop, such as generalized pustulosis or painful cutaneous blisters, refer the patient to a dermatologist.	1 to 3 years	None	Lack of knowledge of guideline. Lack of experience for recognizing late hypersensitivity reactions after contrast administrations.	Lack of knowledge of guideline.	Disseminations of guideline	NVvR	

[1] Barriers can be found at multiple levels. They can exist at the level of the consultant, the hospital organisation, and the health care system.

[2] Actions needed for implementation, but also actions to promote implementation. Think about checks during quality visits, guideline publication, information of hospital management, etcetera.

[3] Who is responsible for implementation of recommendations will largely be determined by the level where the barriers are expected to be.

Evidence Tables

Not applicable.

Exclusion Table

Author and Year	Reason for exclusion
Bellin (2011)	Does not fulfill selection criteria. No control group. Descriptive.
Brockow K (2011)	Does not fulfill selection criteria. No control group. Descriptive.
Christiansen C (2000)	Does not fulfill selection criteria. No control group. Descriptive.
Egbert (2014)	Does not fulfill selection criteria. No control group. Descriptive.
Fok (2017)	Does not fulfill selection criteria. No control group. Descriptive.
Goksel (2011)	Does not fulfill selection criteria. No control group. Descriptive.
Hasdenteufel (2011)	Does not fulfill selection criteria. No control group. Descriptive.
Hash (1999)	Does not fulfill selection criteria. No control group. Descriptive.
Idée JM (2015)	Does not fulfill selection criteria. No control group. Descriptive.
Mikkonen (1995)	Does not fulfill selection criteria. No control group. Descriptive.
Newmark JL (2012)	Does not fulfill selection criteria. No control groep. Descriptive.
Rosado Ingelmo (2016)	Does not fulfill selection criteria. No control group. Descriptive.
Scherer K (2010)	Does not fulfill selection criteria. No control group. Descriptive.
Seitz CS (2009)	Does not fulfill selection criteria. No control group. Descriptive.
Stovsky MD (1995)	Does not fulfill selection criteria. No control group. Descriptive.
Webb JAW (2003)	Does not fulfill selection criteria. No control group. Descriptive.

Literature search

Database	Search string	Total
PubMed 1985 – 3th of January 2018	((((((("Contrast Media"[Majr] OR contrast medi* [ti] OR contrast agent* [ti] OR contrast material* [ti] OR contrast dose [ti] OR contrast doses [ti] OR contrast dosage [ti] OR radiocontrast medi* [ti] OR radiocontrast agent* [ti] OR radiopaque medi* [ti] OR radiocontrast dose [ti] OR radiocontrast doses [ti] OR radiocontrast dosage [ti] OR "Barium"[Mesh] OR barium [tiab] OR gadolinium [tiab] OR microbubble* [tiab]))) AND ((("Drug Hypersensitivity"[Mesh] OR hypersensitiv* [tiab] OR allerg* [tiab] OR anaphylax* [tiab] OR anaphylact* [tiab] OR "Exanthema"[Mesh] OR exanthem* [tiab] OR rash [tiab] OR adverse reaction*[tiab] OR urticaria* [tiab] OR erythem* [tiab] OR hypotension [tiab] OR hypertension [tiab] OR "Stevens-Johnson Syndrome"[Mesh] OR stevens johnson syndrome [tiab] OR sjs [tiab] OR toxic epidermal necrolys* [tiab] OR "Drug Hypersensitivity Syndrome"[Mesh] OR dress syndrome [tiab] OR iodide mump* [tiab]) AND (late [tiab] OR delayed [tiab] OR nonimmediate [tiab])) OR late reaction* [tiab] OR delayed reaction* [tiab] OR nonimmediate reaction* [tiab]))) AND (("english"[Language]) AND ("1985"[Date - Publication] : "3000"[Date - Publication]))) = 320	419
Embase (Elsevier)	(('contrast medium'/exp/mj OR (((contrast OR radiocontrast) NEAR/2 (medi* OR agent* OR material* OR dose OR doses OR dosage)):ti) OR 'radiopaque medi*':ab,ti OR 'barium'/exp/mj OR barium:ab,ti OR 'gadolinium'/exp/mj OR gadolinium:ab,ti OR 'microbubble'/exp/mj OR microbubble*:ab,ti) AND (('hypersensitivity'/exp OR hypersensitiv*:ab,ti OR anaphylax*:ab,ti OR allerg*:ab,ti OR 'rash'/exp OR rash:ab,ti OR 'adverse reaction*':ab,ti OR hypotension:ab,ti OR hypertension:ab,ti OR urticaria*:ab,ti OR erythem*:ab,ti OR exanthem*:ab,ti OR 'stevens johnson syndrome'/exp OR 'stevens johnson syndrome':ab,ti OR sjs:ab,ti OR 'toxic epidermal necrolysis'/exp OR 'toxic epidermal necrolys*':ab,ti OR 'dress syndrome'/exp OR 'dress syndrome':ab,ti OR 'iodide mump*':ab,ti) AND (late:ab,ti OR delayed:ab,ti OR nonimmediate:ab,ti) OR (((late OR delayed OR nonimmediate) NEAR/2 reaction*):ab,ti))) AND [english]/lim AND [1985-2018]/py NOT 'conference abstract':it NOT (('animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp) =370	

Appendices to module 3

Knowledge gaps

It is not clear whether serum tests for hypersensitivity reactions after contrast administration lead to a better probability of a correct diagnosis, and ultimately, a better patient outcome (measured as less recurrent hypersensitivity reactions after contrast administration, less morbidity and mortality).

Indicators

None.

Implementation plan

Recommendation	Time frame for implementation: <1 year, 1 to 3years or >3 years	Expected effect on costs	Limitations for implementation	Barriers to implementation[1]	Actions needed for implementation[2]	Parties responsible for actions[3]	Other remarks
Do not perform a Basophil Activation Test routinely in all patients with a history of hypersensitivity reactions receiving contrast medium.	1 to 3 years	Increase in costs for performing laboratory tests, however lower costs in the future, because recurrent hypersensitivity reactions after contrast medium administration could be prevented.	Lack of knowledge and experience for performing serum tests after contrast medium administration	Lack of knowledge and experience for performing serum tests after hypersensitivity reactions contrast medium administration	Dissemination of guideline Training of radiological personnel to routinely perform laboratory tests after hypersensitivity reactions contrast medium administration	NVvR	
Measure serum tryptase between 1-2 hours from the start of all moderately severe to severe acute hypersensitivity reactions to contrast media.	1 to 3 years	Increase in costs for performing laboratory tests, however lower costs in the future, because recurrent hypersensitivity reactions after contrast medium administrat	Lack of knowledge and experience for performing serum tests after contrast medium administration	Lack of knowledge and experience for performing serum tests after hypersensitivity reactions contrast medium administration	Dissemination of guideline Training of radiological personnel to routinely perform laboratory tests after hypersensitivity reactions contrast medium administration	NVvR	

		ion could be prevented.					
When tryptase is elevated, refer the patient to a drug allergy specialist.	1 to 3 years	Increase in costs for performing laboratory tests, however lower costs in the future, because recurrent hypersensitivity reactions after contrast medium administration could be prevented.	Lack of knowledge and experience for performing serum tests after contrast medium administration	Lack of knowledge and experience for performing serum tests after hypersensitivity reactions contrast medium administration	Dissemination of guideline Training of radiological personnel to routinely perform laboratory tests after hypersensitivity reactions contrast medium administration	NVvR	

[1] Barriers can be found at multiple levels. They can exist at the level of the consultant, the hospital organisation, and the health care system.
[2] Actions needed for implementation, but also actions to promote implementation. Think about checks during quality visits, guideline publication, information of hospital management, et cetera.
[3] Who is responsible for implementation of recommendations will largely be determined by the level where the barriers are expected to be.

Evidence tables

Not applicable.

Exclusion table

Author and Year	Reason for exclusion
Böhm, 2005	Narrative review
Bonadonna, 2016	Narrative review
Comment, 2014	Postmortem study, therefore no provocation test and diagnostic accuracy
Fellinger, 2013	No provocation test and diagnostic accuracy
Fisher, 1998	Patientsgroup does not include patients with a reaction to CM
Górska, 2015	Not the right patient group, no provocation test and diagnostic accuracy
Keyzer, 1984	Does not answer research question
Montañez, 2017	Narrative review.
Palmiere, 2014a	Postmortem study, therefore no provocation test and diagnostic accuracy
Palmiere, 2014b	Narrative review and results postmortem study, no diagnostic accuracy
Srivasta, 2014	Patientgroup includes only one patients with a reaction to CM
Ye, 2014	Investigating causes of anaphylaxis
Zhai, 2017	No provocation test and diagnostic accuracy

Search criteria

Database	Zoektermen	Totaal
PubMed 1985 – januari 2018	((("Contrast Media"[Mesh] OR contrast medi* [tiab] OR contrast agent* [tiab] OR contrast material* [tiab] OR contrast dose [tiab] OR contrast doses [tiab] OR contrast dosage [tiab] OR radiocontrast medi* [tiab] OR radiocontrast agent* [tiab] OR radiopaque medi* [tiab] OR radiocontrast dose [tiab] OR radiocontrast doses [tiab] OR radiocontrast dosage [tiab] OR "Barium"[Mesh] OR barium [tiab] OR gadolinium [tiab] OR microbubble* [tiab]) AND ("Drug Hypersensitivity"[Mesh] OR hypersensitiv* [tiab] OR allerg* [tiab] OR anaphyla* [tiab] OR "Exanthema"[Mesh] OR exanthem* [tiab] OR rash [tiab] OR adverse	368

	reaction*[tiab] OR drug reaction* [tiab] OR urticaria* [tiab] OR erythem* [tiab] OR edema [tiab] OR angioedema [tiab] OR bronchospasm* [tiab] OR hypotension [tiab] OR hypertension [tiab] OR cardiac arrest* [tiab] OR respiratory arrest [tiab] OR "Stevens-Johnson Syndrome"[Mesh] OR stevens johnson syndrome [tiab] OR sjs [tiab] OR toxic epidermal necrolys* [tiab] OR "Drug Hypersensitivity Syndrome"[Mesh] OR dress syndrome [tiab] OR iodide mump* [tiab] OR ((late [tiab] OR delayed [tiab] OR nonimmediate [tiab] OR immediate [tiab] OR acute [tiab] OR severe [tiab]) AND (reaction* [tiab]))) AND (serum hypersensitivity test* [tiab] OR "Immunoglobulin E"[Mesh] OR IgE [tiab] OR "Tryptases"[Mesh] OR tryptase* [tiab] OR urinary histamine metabolite* [tiab] OR "Methylhistamines"[Mesh] OR methylhistamine* [tiab] OR methylimidazole acetic acid* [tiab] OR basophil activation test* [tiab])) AND (("english"[Language]) AND ("1985"[Date - Publication] : "3000"[Date - Publication]))) = 145	
Embase (Elsevier)	(('contrast medium'/exp OR (((contrast OR radiocontrast) NEAR/2 (medi* OR agent* OR material* OR dose OR doses OR dosage)):ab,ti) OR 'radiopaque medi*':ab,ti OR 'barium'/exp OR barium:ab,ti OR 'gadolinium'/exp OR gadolinium:ab,ti OR 'microbubble'/exp OR microbubble*:ab,ti) AND ('hypersensitivity'/exp OR hypersensitiv*:ab,ti OR anaphyla*:ab,ti OR allerg*:ab,ti OR 'rash'/exp OR rash:ab,ti OR 'adverse reaction*':ab,ti OR 'drug reaction*':ab,ti OR urticaria*:ab,ti OR erythem*:ab,ti OR exanthem*:ab,ti OR edema:ab,ti OR angioedema:ab,ti OR bronchospasm*:ab,ti OR 'anaphylactic shock':ab,ti OR hypotension:ab,ti OR hypertension:ab,ti OR 'cardiac arrest':ab,ti OR 'respiratory arrest':ab,ti OR 'stevens johnson syndrome'/exp OR 'stevens johnson syndrome':ab,ti OR sjs:ab,ti OR 'toxic epidermal necrolysis'/exp OR 'toxic epidermal necrolys*':ab,ti OR 'dress syndrome'/exp OR 'dress syndrome':ab,ti OR 'iodide mump*':ab,ti OR (((late OR delayed OR nonimmediate OR immediate OR acute OR severe) NEAR/2 reaction*):ab,ti)) AND (‘serum hypersensitivity test*’:ab,ti OR 'immunoglobulin E'/exp OR IgE:ab,ti OR 'tryptase'/exp OR tryptase*:ab,ti OR ‘urinary histamine metabolite*’:ab,ti OR 'methylhistamine'/exp OR methylhistamine*:ab,ti OR ‘methylimidazole acetic acid*’:ab,ti OR 'basophil activation test'/exp OR ‘basophil activation test*’:ab,ti)) AND [english]/lim AND [1985-2018]/py NOT 'conference abstract':it NOT (('animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp) = 334	

Appendices to module 4

Knowledge gaps

It is unclear whether application of cutaneous tests (skin test, patch test (PT), Intradermal test (IDT), skin prick test (SPT) or scratch test) in patients who have had an acute hypersensitivity reaction after contrast medium administration leads to a better correctly confirmed diagnosis of hypersensitivity reaction.

It is unclear which contrast media should be included in a panel for cutaneous tests.

Indicators

None.

Implementation plan

Recommendation	Time frame for implementation: <1 year, 1 to 3years or >3 years	Expected effect on costs	Limitations for implementation	Barriers to implementation[1]	Actions needed for implementation[2]	Parties responsible for actions[3]	Other remarks
Do not perform skin tests routinely after every hypersensitivity reaction to a contrast medium.	1 to 3 years	None	Lack of knowledge of guideline. Lack of experience for recognizing late hypersensitivity reactions after contrast administrations.	Lack of knowledge of guideline.	Disseminations of guideline	NVvR	
Refer the patient to a specialist in drug allergy to perform skin tests within 6 months after the hypersensitivity reaction in the following patient groups: • Severe hypersensitivity reactions to a contrast medium. • Hypersensitivity reactions with	1 to 3 years	None	Lack of knowledge of guideline. Lack of experience for recognizing late hypersensitivity reactions after contrast administrations.	Lack of knowledge of guideline.	Disseminations of guideline	NVvR	

increased tryptase levels. • Hypersensitivity reactions to 2 or more different contrast media of the same type (e.g. 2 different iodine-based CM) or to 2 or more types of contrast media (e.g. iodine-based CM and gadolinium-based CA). • Specify the used contrast agent in the referral.							
Refer the patient to a specialist in drug allergy to perform skin tests in all patients with breakthrough hypersensitivity reactions despite premedication with corticosteroids and H1-antihistamines.	1 to 3 years	None	Lack of knowledge of guideline. Lack of experience for recognizing late hypersensitivity reactions after contrast administrations.	Lack of knowledge of guideline.	Disseminations of guideline	NVvR	

[1] Barriers can be found at multiple levels. They can exist at the level of the consultant, the hospital organisation, and the health care system.
[2] Actions needed for implementation, but also actions to promote implementation. Think about checks during quality visits, guideline publication, information of hospital management, et cetera.
[3] Who is responsible for implementation of recommendations will largely be determined by the level where the barriers are expected to be.

Evidence tables

Evidence table for diagnostic test accuracy studies

Study reference	Study characteristics	Patient characteristics	Index test (Test of interest)	Reference test	Follow-up	Outcome measures and effect size	Comments
Caimmi, 2010	Type of study[1]: Case-control cohort Setting: Hospital Country: France Conflicts of interest: None	Inclusion criteria: NR Exclusion criteria: NR N=159 Median age [range]: 56 years [45-65] Sex: 60% F	Describe index test: Skin test Cut-off point(s): Skin test positivity was determined when the diameter of the wheal increased by at least 3 mm, and surrounding erythema was observed after 15 to 20 minutes Comparator test[2]: NR Cut-off point(s): NR	Describe reference test[3]: Provocation Negative skin test Cut-off point(s): NR	Time between the index test en reference test: NR For how many participants were no complete outcome data available? N (100%)	Outcome measures and effect size (include 95%CI and p-value if available)[4]: Negative predictive value skintest: 96.6% (95% CI: 89.9–103.2)	Clinical testing for ICM hypersensitivity has a negative predictive value of 96.6% (95% CI: 89.9–103.2) and none of the reactions in skin-test-negative patients were severe. Multi-centric large surveys are still needed for confirmation
Kim, 2013	Type of study: Prospective follow-up. Setting: Hospital	Inclusion criteria: We prospectively enrolled patients who were to undergo CT using RCM at Seoul National University Bundang Hospital	Describe index test: Skin test Cut-off point(s): Skin test positivity was determined when the	Describe reference test: Provocation to CM by Negative skin test	Time between the index test en reference test: For how many participants were no complete	Outcome measures and effect size (include 95%CI and p-value if available):	RCM skin testing for screening is of no clinical utility in predicting hypersensitivity reactions. RCM skin testing may have modest utility in retrospectively evaluating severe adverse reactions.

[1] In case of a case-control design the patient characteristics should be described per group (cases en controls). NB; case control studies will overestimate the accuracy (Lijmer et al., 1999).

[2] Comparator test is comparable to the C from the PICO of an intervention question. Severla tests can also be compared. Add this as comparator test 2 etcetera. Attention: the comparator test can never be the reference standard.

[3] The reference standard is the test that definitely demonstrates if one has the disease or not. Ideally the reference standard is the Gold standard (100% sensitive and 100% specific). Attention: the reference standard can never be the comparator test.

[4] Describe the statistical parameters fort he comparison of the index test with the reference test, and fort he ocmparison between index tests.

	Country: Korea Conflicts of interest: NR	from July to November 2010. Exclusion criteria: Patients who did not consent to the study or who had been administered premedications, such as steroids, antihistamines, or other medications that may have affected the skin test results, were excluded from the study N=1048 Mean age ± SD: 55.1 years (14.5) Sex: 48% M	diameter of the wheal increased by at least 3 mm, and surrounding erythema was observed after 15 to 20 minutes Cut-off point(s): NR	Cut-off point(s): NR	outcome data available? N (100%)	Negative predictive value skintest: 80%	
Salas, 2013	Type of study: Retrospective study Setting: Hospital Country: Spain Conflicts of interest: None	Inclusion criteria: NR Exclusion criteria: NR N=90 Mean age: 54.5 years (SD 27) Sex: 60% F	Describe index test: Skin test Cut-off point(s): NR Comparator test: basophil activation test (BAT) Cut-off point(s): NR	Describe reference test: Provocation test Cut-off point(s): NR	Time between the index test en reference test: NR For how many participants were no complete outcome data available? N=11 (17%) Reasons for incomplete	Outcome measures and effect size (include 95%CI and p-value if available): Negative predictive value skintest: 91%	ST or DPT. BAT proved a valuable method for diagnosis confirmed hypersensitivity to RCM in 9%.

					outcome data described? NR		
Sesé, 2016	Type of study: Retrospective study Setting: Hospital Country: France Conflicts of interest: None	Inclusion criteria: NR Exclusion criteria: NR N=37 Mean age: 54.5 years (SD 27) Sex: 65% F	Describe index test: Skin test Cut-off point(s): least 3 mm in diameter with erythema Comparator test: NR Cut-off point(s): NR	Describe reference test: Provocation test Cut-off point(s): NR	Time between the index test en reference test: NR For how many participants were no complete outcome data available? (100%)	Outcome measures and effect size (include 95%CI and p-value if available): Negative predictive value skintest: 80%	For immediate hypersensitivity reaction to ICM, the NPV for skin tests and IPT with low dose was 80% (95% CI 44–97%).
Torres, 2012	Type of study: Retrospective study Setting: Hospital Country: Spain Conflicts of interest: NR	Inclusion criteria: NR Exclusion criteria: NR N=161 Mean age: 58.5 years (IR: 48-67)) Sex: 51% M	Describe index test: Skin test Cut-off point(s): least 3 mm in diameter with erythema Comparator test: NR Cut-off point(s): NR	Describe reference test: Provocation test Cut-off point(s): NR	Time between the index test en reference test: NR For how many participants were no complete outcome data available? (100%)	Outcome measures and effect size (include 95%CI and p-value if available): Negative predictive value skintest: 65.4%	Patients with nonimmediate reactions to CM were identified by skin testing in 43.6% and by DPT in 56.4%. The method to confirm the diagnosis differed depending on the CM involved

Risk of bias assessment diagnostic accuracy studies (QUADAS II, 2011)

Study reference	Patient selection	Index test	Reference standard	Flow and timing	Comments with respect to applicability
Caimmi, 2010	Was a consecutive or random sample of patients enrolled? Unclear Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? Yes	Were the index test results interpreted without knowledge of the results of the reference standard? No If a threshold was used, was it pre-specified? No	Is the reference standard likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index test? Unclear	Was there an appropriate interval between index test(s) and reference standard? Yes Did all patients receive a reference standard? No Did patients receive the same reference standard? Yes Were all patients included in the analysis? Yes	Are there concerns that the included patients do not match the review question? Unclear Are there concerns that the index test, its conduct, or interpretation differ from the review question? No Are there concerns that the target condition as defined by the reference standard does not match the review question? Unclear
	CONCLUSION: Could the selection of patients have introduced bias? **RISK: LOW/HIGH/UNCLEAR**	CONCLUSION: Could the conduct or interpretation of the index test have introduced bias? **RISK: LOW /HIGH/UNCLEAR**	CONCLUSION: Could the reference standard, its conduct, or its interpretation have introduced bias? **RISK: LOW /HIGH/UNCLEAR**	CONCLUSION Could the patient flow have introduced bias? **RISK: HIGH**	
Kim, 2013	Was a consecutive or random sample of patients enrolled? Unclear Was a case-control design avoided? Unclear Did the study avoid inappropriate exclusions? Yes	Were the index test results interpreted without knowledge of the results of the reference standard? Unclear If a threshold was used, was it pre-specified? Unclear	Is the reference standard likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index test? Unclear	Was there an appropriate interval between index test(s) and reference standard? Yes Did all patients receive a reference standard? No Did patients receive the same reference standard?	Are there concerns that the included patients do not match the review question? No Are there concerns that the index test, its conduct, or interpretation differ from the review question? No

				Yes Were all patients included in the analysis? Yes	Are there concerns that the target condition as defined by the reference standard does not match the review question? No
	CONCLUSION: Could the selection of patients have introduced bias? **RISK: LOW/HIGH/UNCLEAR**	CONCLUSION: Could the conduct or interpretation of the index test have introduced bias? **RISK: LOW /HIGH/UNCLEAR**	CONCLUSION: Could the reference standard, its conduct, or its interpretation have introduced bias? **RISK: LOW /HIGH/UNCLEAR**	CONCLUSION Could the patient flow have introduced bias? **RISK: LOW /HIGH/UNCLEAR**	
Salas, 2013	Was a consecutive or random sample of patients enrolled? Unclear Was a case-control design avoided? Unclear Did the study avoid inappropriate exclusions? Yes	Were the index test results interpreted without knowledge of the results of the reference standard? Unclear If a threshold was used, was it pre-specified? Unclear	Is the reference standard likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index test? Unclear	Was there an appropriate interval between index test(s) and reference standard? Yes Did all patients receive a reference standard? No Did patients receive the same reference standard? Yes Were all patients included in the analysis? Yes	Are there concerns that the included patients do not match the review question? No Are there concerns that the index test, its conduct, or interpretation differ from the review question? No Are there concerns that the target condition as defined by the reference standard does not match the review question? Unclear
	CONCLUSION: Could the selection of patients have introduced bias? **RISK: LOW/HIGH/UNCLEAR**	CONCLUSION: Could the conduct or interpretation of the index test have introduced bias? **RISK: LOW /HIGH/UNCLEAR**	CONCLUSION: Could the reference standard, its conduct, or its interpretation have introduced bias? **RISK: LOW /HIGH/UNCLEAR**	CONCLUSION Could the patient flow have introduced bias? **RISK: LOW /HIGH/UNCLEAR**	
Sesé, 2016	Was a consecutive or random sample of patients enrolled?	Were the index test results interpreted without knowledge	Is the reference standard likely to correctly classify the target	Was there an appropriate interval between index test(s)	Are there concerns that the included patients do not match

	Unclear Was a case-control design avoided? Unclear Did the study avoid inappropriate exclusions? Yes	of the results of the reference standard? Unclear If a threshold was used, was it pre-specified? Unclear	condition? Yes Were the reference standard results interpreted without knowledge of the results of the index test? Unclear	and reference standard? Yes Did all patients receive a reference standard? No Did patients receive the same reference standard? Yes Were all patients included in the analysis? Yes	the review question? No Are there concerns that the index test, its conduct, or interpretation differ from the review question? No Are there concerns that the target condition as defined by the reference standard does not match the review question? No
	CONCLUSION: Could the selection of patients have introduced bias? **RISK: LOW/HIGH/UNCLEAR**	CONCLUSION: Could the conduct or interpretation of the index test have introduced bias? **RISK: LOW /HIGH/UNCLEAR**	CONCLUSION: Could the reference standard, its conduct, or its interpretation have introduced bias? **RISK: LOW /HIGH/UNCLEAR**	CONCLUSION Could the patient flow have introduced bias? **RISK: LOW /HIGH/UNCLEAR**	
Torres, 2012	Was a consecutive or random sample of patients enrolled? Unclear Was a case-control design avoided? Unclear Did the study avoid inappropriate exclusions? Yes	Were the index test results interpreted without knowledge of the results of the reference standard? Unclear If a threshold was used, was it pre-specified? Unclear	Is the reference standard likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index test? Unclear	Was there an appropriate interval between index test(s) and reference standard? Yes Did all patients receive a reference standard? No Did patients receive the same reference standard? Yes Were all patients included in the analysis? Yes	Are there concerns that the included patients do not match the review question? No Are there concerns that the index test, its conduct, or interpretation differ from the review question? No Are there concerns that the target condition as defined by the reference standard does not match the review question? No
	CONCLUSION:	CONCLUSION:	CONCLUSION:	CONCLUSION	

	Could the selection of patients have introduced bias? **RISK: LOW/HIGH/UNCLEAR**	Could the conduct or interpretation of the index test have introduced bias? **RISK: LOW /HIGH/UNCLEAR**	Could the reference standard, its conduct, or its interpretation have introduced bias? **RISK: LOW /HIGH/UNCLEAR**	Could the patient flow have introduced bias? **RISK: LOW /HIGH/UNCLEAR**	

Judgments on risk of bias are dependent on the research question: some items are more likely to introduce bias than others, and may be given more weight in the final conclusion on the overall risk of bias per domain:

Patient selection:
Consecutive or random sample has a low risk to introduce bias.
A case control design is very likely to overestimate accuracy and thus introduce bias.
Inappropriate exclusion is likely to introduce bias.

Index test:
This item is similar to "blinding" in intervention studies. The potential for bias is related to the subjectivity of index test interpretation and the order of testing.
Selecting the test threshold to optimise sensitivity and/or specificity may lead to overoptimistic estimates of test performance and introduce bias.

Reference standard:
When the reference standard is not 100% sensitive and 100% specific, disagreements between the index test and reference standard may be incorrect, which increases the risk of bias.
This item is similar to "blinding" in intervention studies. The potential for bias is related to the subjectivity of index test interpretation and the order of testing.

Flow and timing:
If there is a delay or if treatment is started between index test and reference standard, misclassification may occur due to recovery or deterioration of the condition, which increases the risk of bias.

If the results of the index test influence the decision on whether to perform the reference standard or which reference standard is used, estimated diagnostic accuracy may be biased.
All patients who were recruited into the study should be included in the analysis, if not, the risk of bias is increased.

Judgement on applicability:
Patient selection: there may be concerns regarding applicability if patients included in the study differ from those targeted by the review question, in terms of severity of the target condition, demographic features, presence of differential diagnosis or co-morbidity, setting of the study and previous testing protocols.

Index test: if index tests methods differ from those specified in the review question there might be concerns regarding applicability.
Reference standard: the reference standard may be free of bias but the target condition that it defines might differ from the target condition specified in the review question

Search criteria

Database	Search terms	Totaal
PubMed 1985 – januari 2018	(("Contrast Media"[Mesh] OR contrast medi* [tiab] OR contrast agent* [tiab] OR contrast material* [tiab] OR contrast dose [tiab] OR contrast doses [tiab] OR contrast dosage [tiab] OR radiocontrast medi* [tiab] OR radiocontrast agent* [tiab] OR radiopaque medi* [tiab] OR radiocontrast dose [tiab] OR radiocontrast doses [tiab] OR radiocontrast dosage [tiab] OR "Barium"[Mesh] OR barium [tiab] OR gadolinium [tiab] OR microbubble* [tiab]) AND ("Drug Hypersensitivity"[Mesh] OR hypersensitiv* [tiab] OR allerg* [tiab] OR anaphyla* [tiab] OR "Exanthema"[Mesh] OR exanthem* [tiab] OR rash [tiab] OR adverse reaction*[tiab] OR drug reaction* [tiab] OR urticaria* [tiab] OR erythem* [tiab] OR edema [tiab] OR angioedema [tiab] OR bronchospasm* [tiab] OR hypotension [tiab] OR hypertension [tiab] OR cardiac arrest* [tiab] OR respiratory arrest [tiab] OR "Stevens-Johnson Syndrome"[Mesh] OR stevens johnson syndrome [tiab] OR sjs [tiab] OR toxic epidermal necrolys* [tiab] OR "Drug Hypersensitivity Syndrome"[Mesh] OR dress syndrome [tiab] OR iodide mump* [tiab] OR ((late [tiab] OR delayed [tiab] OR nonimmediate [tiab] OR immediate [tiab] OR acute [tiab] OR severe [tiab]) AND (reaction* [tiab]))) AND ("Skin Tests"[Mesh] OR skin test* [tiab] OR cutaneous test* [tiab] OR skin test* [tiab] OR patch test* [tiab] OR intradermal test* [tiab] OR prick test* [tiab] OR scratch test* [tiab]) AND (("english"[Language]) AND ("1985"[Date - Publication] : "3000"[Date - Publication]))) = 158	358
Embase (Elsevier)	(('contrast medium'/exp OR (((contrast OR radiocontrast) NEAR/2 (medi* OR agent* OR material* OR dose OR doses OR dosage)):ab,ti) OR 'radiopaque medi*':ab,ti OR 'barium'/exp OR barium:ab,ti OR 'gadolinium'/exp OR gadolinium:ab,ti OR 'microbubble'/exp OR microbubble*:ab,ti) AND ('hypersensitivity'/exp OR hypersensitiv*:ab,ti OR anaphyla*:ab,ti OR allerg*:ab,ti OR 'rash'/exp OR rash:ab,ti OR 'adverse reaction*':ab,ti OR 'drug reaction*':ab,ti OR urticaria*:ab,ti OR erythem*:ab,ti OR exanthem*:ab,ti OR edema:ab,ti OR angioedema:ab,ti OR bronchospasm*:ab,ti OR 'anaphylactic shock':ab,ti OR hypotension:ab,ti OR hypertension:ab,ti OR 'cardiac arrest':ab,ti OR 'respiratory arrest':ab,ti OR 'stevens johnson syndrome'/exp OR 'stevens johnson syndrome':ab,ti OR sjs:ab,ti OR 'toxic epidermal necrolysis'/exp OR 'toxic epidermal necrolys*':ab,ti OR 'dress syndrome'/exp OR 'dress syndrome':ab,ti OR 'iodide mump*':ab,ti OR (((late OR delayed OR nonimmediate OR immediate OR acute OR severe) NEAR/2 reaction*):ab,ti)) AND ('skin test'/exp OR 'cutaneous test*':ab,ti OR 'skin test*':ab,ti OR 'patch test*':ab,ti OR 'intradermal test*':ab,ti OR 'prick test*':ab,ti OR 'scratch test*':ab,ti)) AND [english]/lim AND [1985-2018]/py NOT 'conference abstract':it NOT (('animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp) = 330	

Table: Exclusion after revision of full text

Author and year	Reason for exclusion
Ahn, 2015	Study does not meet the PICO criteria; no reference test was used to confirm response on skintest (provocation test)
Barbaud, 2014	Literature overview does not meet the PICO criteria
Berti, 2016	Study does not meet the PICO criteria
Brockow, 1999	Case report (n=1)
Brockow, 2009	Case report study (n=1)
Cabenas, 2017	Evalaution of the diagnostic properties of the Lymphocytic transformation test (i) for drug-induced reactions.
Carr, 2016	Literature overview does not meet the PICO criteria
Chiriac, 2011	Study does not meet the PICO criteria; no provocation test to confirm skin test results
Chirumbolo, 2013	Study does not meet the PICO criteria; diagnostic properties of the Basophil activation test (BAT)
Della-Torre, 2015	Study does not meet the PICO criteria; no reference test was used to confirm response on skintest (provocation test)
Goksel, 2011	Study does not meet the PICO criteria; no provocation test to confirm skin testing results
Gómez, 2013	Literature overview (no systematic review)
Hasdenteufel, 2011	Study does not meet the PICO criteria; no provocation test to confirm skin testing results
Kim, 2014	Study does not meet the PICO criteria; case control study on clinical outcome and characteristics following skin testing.
Kvedariene, 2006	Study does not meet the PICO criteria; comparison of patients with postive and negative ICM skin tets (no diagnostic evaluation)
Lerch, 2007	Caseseries report (n=2)
Lerondeau, 2016	Letter to the Editor
Mangodt, 2015	Study does not meet the PICO criteria; diagnostic properties of Basophil Activation Test
Morales-Cabeza, 2017	No evaluation of diagnostic properties of tests but evaluating the clinical and allergologic features of IHRs to ICMs.
Nyfeler, 1997	Study does not meet the PICO criteria; no evaluation of radiocontrast media reaction
Ohtoshi, 2014	Study does not meet the PICO criteria; no provocation test to confirm Patch testing results
Prieto-García, 2013	Study describes characteristics and does not analyze diagnostic properties of skin tests
Ramirez, 2014	Study does not meet the PICO criteria. The study objective was to determine risk factors for hypersensitivity reaction to CM.
Renaudin, 2013	Study does not meet the PICO criteria; no provocation test to confirm Patch testing results
Seitz, 2009	Study does not meet the PICO criteria; no evaluation of diagnostic properties of skin tests
Soyyiğit, 2016	Study does not meet the PICO criteria (no provocation test)
Steiner, 2016	Literature overview to evaluate the suitability of Basophil Acivation Test as biomarker for

	the diagnosis of immediate drug-induced hypersensitivity reactions (no data collection)
Tepetam, 2016	Study does not meet the PICO criteria; no reference test was used to confirm response on skintest (provocation test)
Trcka, 2008	Study does not meet the PICO criteria; no evaluation of diagnostic properties of skin tests
Vernassiere, 2004	Study does not meet the PICO criteria; no evaluation of diagnostic properties of skin tests
Waton, 2009	Study does not meet the PICO criteria; diagnostic properties of drug skin tests (no CMR)
Yoon, 2015	Included cases series en exploratory findings in analyses

Appendices to module 5

Knowledge gaps

What factors are related to an increased risk of developing hypersensitivity reactions after contrast administration?

What are the effects of a prophylactic measure to prevent hypersensitivity reactions after contrast administration compared to a different / control measure to prevent hypersensitivity reactions after contrast administration or to no prophylactic measure, in patients undergoing radiological examinations with contrast media?

Indicators

Every department should have a local protocol in place detailing the follow-up management of a patient that has had a hypersensitivity reaction after contrast media.

1. Hospital-wide protocols about follow-up management of a patient that has had a hypersensitivity reaction after contrast media	
Operationalization	Is there an overall hospital-wide protocol or process-agreement on the follow-up management of a patient that has had a hypersensitivity reaction after contrast media.
Numerator	Not applicable
Denominator	Not applicable
Type of indicator	Input
In- and exclusion criteria	Inclusion A hospital-wide protocol, on the follow-up management of a patient that has had a hypersensitivity reaction after contrast media
Quality domain	Safety and effectivity
Measuring frequency	Once a year
Report year	2020
Frequency of report	Once a year

Each hospital should register which contrast medium is used at every examination, and in what amount.

2. Registration of type and amount of contrast medium used at every examination with contrast	
Operationalization	Is the type and amount of contrast medium used at every examination with contrast systematically registered in the electronic patient dossier?
Numerator	Not applicable
Denominator	Not applicable
Type of indicator	Input
In- and exclusion criteria	Inclusion Systematic registration of type and amount of contrast medium of every examination with contrast in the electronic patient dossier.
Quality domain	Safety and effectivity
Measuring frequency	Once a year

Report year	2020
Frequency of report	Once a year

Implementation plan

Recommendation	Time frame for implementation: <1 year, 1 to 3years or >3 years	Expected effect on costs	Limitations for implementation	Barriers to implementation[1]	Actions needed for implementation[2]	Parties responsible for actions[3]	Other remarks
Patients with a hypersensitivity reaction to an **known ICM or GBCA** *Elective (plannable) examinations with ICM or GBCA*							
In all patients with a (documented) history of a hypersensitivity reaction to an iodine-based or gadolinium-based CM, consider an alternative imaging modality. When this is not possible, consider performing unenhanced exam, if this has an acceptable reduction in diagnostic quality.	1 to 3 years	None	Lack of knowledge of guideline.	Lack of knowledge of guideline. No knowledge of the CM that was administered prior tot he hypersensitivity reaction.	Disseminations of guideline	NVvR	
If the previous hypersensitivity reaction was mild: • Choose a different ICM or GBCA* • Observe the patient ≥ 30 min with IV in place • Be vigilant to react to a possible new hypersensitivity reaction	1 to 3 years	None	Lack of knowledge of guideline.	Lack of knowledge of guideline. No knowledge of the CM that was administered prior tot he hypersensitivity reaction.	Disseminations of guideline	NVvR	
If the previous hypersensitivity reaction was moderate: • Choose a different ICM	1 to 3 years	None	Lack of knowledge of guideline.	Lack of knowledge of guideline. No knowledge of the CM that was	Disseminations of guideline	NVvR	

or GBCA* • Observe the patient ≥ 30 min with IV in place • Be vigilant to react to a possible new hypersensitivity reaction In cases of doubtful severity consider referring the patient to a drug allergy specialist for allegologic skin testing with a panel of different iodine-based or gadolinium-based CM.				administered prior tot he hypersensitivity reaction.			
If the previous hypersensitivity reaction was severe: • If clinically reasonable, defer the imaging study until results of allergologic skin testing are available • Refer the patient to a drug allergy specialist for allegologic skin testing with a panel of different iodine-based or gadolinium-based CM • Apply the advice of the drug allergy specialist for choice of alternative CM in future examinations	1 to 3 years	None	Lack of knowledge of guideline.	Lack of knowledge of guideline. No knowledge of the CM that was administered prior tot he hypersensitivity reaction.	Disseminations of guideline	NVvR	

• Premedicate with 2 x 25 mg prednisolone PO/IV** 12h and 2h before CM administration and 2mg clemastine IV within 1h before CM administration. • Observe the patient ≥ 30 min with IV in place • Be vigilant to react to a possible new hypersensitivity reaction							
Acute (within hours) or emergency (direct) examinations with ICM or GBCA							
In all patients with a (documented) history of a hypersensitivity reaction to an iodine-based CM, consider an alternative imaging modality. When this is not possible, consider performing unenhanced exam, if this has an acceptable reduction in diagnostic quality.	1 to 3 years	None	Lack of knowledge of guideline.	Lack of knowledge of guideline. No knowledge of the CM that was administered prior tot he hypersensitivity reaction.	Disseminations of guideline	NVvR	
If the previous hypersensitivity reaction was mild: • Choose a different ICM or GBCA* • Observe the patient ≥ 30 min with IV in place • Be vigilant to react to a possible new hypersensitivity	1 to 3 years	None	Lack of knowledge of guideline.	Lack of knowledge of guideline. No knowledge of the CM that was administered prior tot he hypersensitivity reaction.	Disseminations of guideline	NVvR	

reaction.							
If the previous hypersensitivity reaction was moderate: • Premedicate with 50 mg prednisolone IV** and 2mg clemastine IV within 30min before CM administrationChoose a different ICM or GBCA* • Observe the patient ≥ 30 min with IV in place • Be vigilant to react to a possible new hypersensitivity reaction	1 to 3 years	None	Lack of knowledge of guideline.	Lack of knowledge of guideline. No knowledge of the CM that was administered prior tot he hypersensitivity reaction.	Disseminations of guideline	NVvR	
If the previous hypersensitivity reaction was severe: • Premedicate with 50 mg prednisolone IV** and 2mg clemastine IV within 30min before CM administrationChoose a different ICM or GBCA* • Observe the patient ≥ 30 min with IV in place • Be vigilant to react to a possible new hypersensitivity reaction	1 to 3 years	None	Lack of knowledge of guideline.	Lack of knowledge of guideline. No knowledge of the CM that was administered prior tot he hypersensitivity reaction.	Disseminations of guideline	NVvR	
Patients with a hypersensitivity reaction to an **unknown ICM or GBCA** *Elective (plannable) examinations with ICM or GBCA*							
In all patients with a	1 to 3 years	None	Lack of	Lack of	Disseminations of	NVvR	

(documented) history of a hypersensitivity reaction to an iodine-based or gadolinium-based CM, consider an alternative imaging modality. When this is not possible, consider performing unenhanced exam, if this has an acceptable reduction in diagnostic quality.			knowledge of guideline.	knowledge of guideline. No knowledge of the CM that was administered prior tot he hypersensitivity reaction.	guideline		
If the previous hypersensitivity reaction was mild: • Proceed with the radiologic examination normally • Observe the patient ≥ 30 min with IV in place • Be vigilant to react to a possible new hypersensitivity reaction.	1 to 3 years	None	Lack of knowledge of guideline.	Lack of knowledge of guideline. No knowledge of the CM that was administered prior tot he hypersensitivity reaction.	Disseminations of guideline	NVvR	
If the previous hypersensitivity reaction was moderate: • Proceed with the radiologic examination normally • Observe the patient ≥ 30 min with IV in place • Be vigilant to react to a possible new hypersensitivity reaction.	1 to 3 years	None	Lack of knowledge of guideline.	Lack of knowledge of guideline. No knowledge of the CM that was administered prior tot he hypersensitivity reaction.	Disseminations of guideline	NVvR	

In cases of doubtful severity consider referring the patient to a drug allergy specialist for allergologic skin testing with a panel of different iodine-based or gadolinium-based CM.							
If the previous hypersensitivity reaction was severe: • If clinically reasonable, defer the imaging study until results of allergologic skin testing are available • Refer the patient to a drug allergy specialist for allergologic skin testing with a panel of different iodine-based or gadolinium-based CM • Apply the advice of the drug allergy specialist for choice of alternative CM in future examinations • Premedicate with 2 x 25 mg prednisolone PO/IV** 12h and 2h before CM administration and 2mg clemastine IV within 1h before CM	1 to 3 years	None	Lack of knowledge of guideline.	Lack of knowledge of guideline. No knowledge of the CM that was administered prior tot he hypersensitivity reaction.	Disseminations of guideline	NVvR	

administration. • Observe the patient ≥ 30 min with IV in place • Be vigilant to react to a possible new hypersensitivity reaction.							
Acute (within hours) or emergency (direct) examinations with ICM or GBCA							
In all patients with a (documented) history of a hypersensitivity reaction to an iodine-based or gadolinium-based CM, consider an alternative imaging modality. When this is not possible, consider performing unenhanced exam, if this has an acceptable reduction in diagnostic quality.	1 to 3 years	None	Lack of knowledge of guideline.	Lack of knowledge of guideline. No knowledge of the CM that was administered prior tot he hypersensitivity reaction.	Disseminations of guideline	NVvR	
If the previous hypersensitivity reaction was mild: • Proceed with the radiologic examination normally • Observe the patient ≥ 30 min with IV in place • Be vigilant to react to a possible new hypersensitivity reaction.	1 to 3 years	None	Lack of knowledge of guideline.	Lack of knowledge of guideline. No knowledge of the CM that was administered prior tot he hypersensitivity reaction.	Disseminations of guideline	NVvR	
If the previous hypersensitivity reaction was moderate:	1 to 3 years	None	Lack of knowledge of guideline.	Lack of knowledge of guideline. No knowledge of the	Disseminations of guideline	NVvR	

• Premedicate with 50 mg prednisolone IV** and 2mg clemastine IV within 30min before CM administration Proceed with the radiologic examination normally • Observe the patient ≥ 30 min with IV in place • Be vigilant to react to a possible new hypersensitivity reaction.				CM that was administered prior tot he hypersensitivity reaction.			
If the previous hypersensitivity reaction was severe: • Premedicate with 50 mg prednisolone IV** and 2mg clemastine IV within 30min before CM administration Proceed with the radiologic examination normally • Observe the patient ≥ 30 min with IV in place • Be vigilant to react to a possible new hypersensitivity reaction.	1 to 3 years	None	Lack of knowledge of guideline.	Lack of knowledge of guideline. No knowledge of the CM that was administered prior tot he hypersensitivity reaction.	Disseminations of guideline	NVvR	
Patients with breakthrough reactions to CM							
In patients with breakthrough hypersensitivity reactions to iodine-based or gadolinium-based CM apply	1 to 3 years	None	Lack of knowledge of guideline.	Lack of knowledge of guideline. No knowledge of the CM that was	Disseminations of guideline	NVvR	

the same as above, but always refer the patient to a drug allergy specialist for allergologic skin testing with a panel of different ICM or GBCA.				administered prior tot he hypersensitivity reaction.			
Patients with hypersensitivity reactions to multiple CM							
In patients with hypersensitivity reactions to multiple iodine-based or gadolinium-based CM (either 2 or more different iodine-based CM or gadolinium-based CA or to an iodine-based CM and a gadolinium-based CA) apply the same as above, but always refer the patient to a drug allergy specialist for allergologic skin testing with a panel of different ICM and GBCA.	1 to 3 years	None	Lack of knowledge of guideline.	Lack of knowledge of guideline. No knowledge of the CM that was administered prior tot he hypersensitivity reaction.	Disseminations of guideline	NVvR	
Recommendations Hypersensitivity Reactions after Nonvascular CM Administration							
Small amounts of ICM or GBCA can be absorbed by mucosa and enter the systemic circulation after all types of nonvascular CM administration.	1 to 3 years	None	Lack of knowledge of guideline.	Lack of knowledge of guideline. No knowledge of the CM that was administered prior tot he hypersensitivity reaction.	Disseminations of guideline	NVvR	
Hypersensitivity reactions after nonvascular administration of ICM and GBCA can occur, but their incidence is low to very	1 to 3 years	None	Lack of knowledge of guideline.	Lack of knowledge of guideline. No knowledge of the CM that was	Disseminations of guideline	NVvR	

low.				administered prior tot he hypersensitivity reaction.			
No preventive measures are indicated for ERCP or for nonvascular GBCA administration. For other indications using ICM no firm recommendations can be given for patients that have experienced hypersensitivity reactions to CM in the past.	1 to 3 years	None	Lack of knowledge of guideline.	Lack of knowledge of guideline. No knowledge of the CM that was administered prior tot he hypersensitivity reaction.	Disseminations of guideline	NVvR	
In patients that have experienced *severe* hypersensitivity reactions to CM in the past, alternative imaging or contrast agents should be explored with the radiologist, and a strict indication for examinations using nonvascular CM administration is needed. In patients that have experienced *severe* hypersensitivity reactions to CM in the past, preventive measures for severe reactions as outlined in Module 5 may be followed prior to examinations using nonvascular CM administration, if possible	1 to 3 years	None	Lack of knowledge of guideline.	Lack of knowledge of guideline. No knowledge of the CM that was administered prior tot he hypersensitivity reaction.	Disseminations of guideline	NVvR	

after laboratory and skin testing by a specialist in drug allergy prior to the examination.							

[1] Barriers can be found at multiple levels. They can exist at the level of the consultant, the hospital organisation, and the health care system.

[2] Actions needed for implementation, but also actions to promote implementation. Think about checks during quality visits, guideline publication, information of hospital management, et cetera.

[3] Who is responsible for implementation of recommendations will largely be determined by the level where the barriers are expected to be.

Evidence Tables

Table of quality assessment for systematic reviews of RCTs and observational studies

Based on AMSTAR checklist (Shea, 2007; BMC Methodol 7: 10; doi:10.1186/1471-2288-7-10) and PRISMA checklist (Moher, 2009; PLoS Med 6: e1000097; doi:10.1371/journal.pmed1000097)

Study First author, year	Appropriate and clearly focused question?[1] Yes/no/unclear	Comprehensive and systematic literature search?[2] Yes/no/unclear	Description of included and excluded studies?[3] Yes/no/unclear	Description of relevant characteristics of included studies?[4] Yes/no/unclear	Appropriate adjustment for potential confounders in observational studies?[5] Yes/no/unclear/not applicable	Assessment of scientific quality of included studies?[6] Yes/no/unclear	Enough similarities between studies to make combining them reasonable?[7] Yes/no/unclear	Potential risk of publication bias taken into account?[8] Yes/no/unclear	Potential conflicts of interest reported?[9] Yes/no/unclear
Tramer, 2006	Yes	Yes	Included studies: yes. Excluded studies: no	Yes	Unclear	Unclear	Yes	No	No

1. **Research question (PICO) and inclusion criteria should be appropriate and predefined.**
2. **Search period and strategy should be described; at least Medline searched; for pharmacological questions at least Medline + EMBASE searched.**
3. **Potentially relevant studies that are excluded at final selection (after reading the full text) should be referenced with reasons.**
4. **Characteristics of individual studies relevant to research question (PICO), including potential confounders, should be reported.**
5. **Results should be adequately controlled for potential confounders by multivariate analysis (not applicable for RCTs).**
6. **Quality of individual studies should be assessed using a quality scoring tool or checklist (Jadad score, Newcastle-Ottawa scale, risk of bias table et cetera).**
7. **Clinical and statistical heterogeneity should be assessed; clinical: enough similarities in patient characteristics, intervention and definition of outcome measure to allow pooling? For pooled data: assessment of statistical heterogeneity using appropriate statistical tests (for exampl Chi-square, I^2)?**
8. **An assessment of publication bias should include a combination of graphical aids (for exampl funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test, Hedges-Olken). Note: If no test values or funnel plot included, score "no". Score "yes" if mentions that publication bias could not be assessed because there were fewer than 10 included studies.**
9. **Sources of support (including commercial co-authorship) should be reported in both the systematic review and the included studies. Note: To get a "yes," source of funding or support must be indicated for the systematic review AND for each of the included studies.**

Evidence table for systematic review of RCTs and observational studies (intervention studies)

Research question:

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
Tramer, 2006 [individual study characteristics deduced from [1st author, year of publication]] PS., study characteristics and results are extracted from the SR (unless stated otherwise)	SR and meta-analysis of RCTs *Literature search up to October, 2005* A: Bertrand, 1992 B: Chevrot, 1988 C: Ginsberg, 1996 D: Lasser, 1987 E: Lasser, 1994 F: Ring, 1985 G: Small, 1982 H: Smith, 1995 I: Wicke, 1975 Study design: RCT Setting and Country: Switzerland Source of funding and conflicts of interest: Not reported	Inclusion criteria SR: 1) trials (without language restrictions) that tested premedication in patients who received iodinated contrast media. 2) random allocation of patients, use of premedication alone or in combination, presence of a placebo or a no treatment control group, and reporting of presence or absence of allergic reactions Exclusion criteria SR: Not reported *9 studies*	Describe intervention: A: Hydroxyzine 100 mg PO 12 h before (200) B: Betamethasone 8 mg IV with CM C: Dexamethasone 4 mg PO 4×/d for 24 h (42); D: methylprednisolone 2×32 mg PO evening and 2 h before (2513, group 1); methylprednisolone 32 mg PO 2 h before (1759, group 2); E: methylprednisolone 2×32 mg PO 6-24 h and 2 h before (580); F: Prednisolone 250 mg IV (198); clemastine 0.03 mg/kg IV (191); clemastine 0.03 mg/kg + cimetidine 2-5 mg/kg (according to renal function) IV (196); G: Chlorpheniramine 10 mg SC 15 min before (78); placebo (saline) SC (71);	Describe control: A: placebo B: no treatment C: placebo D: placebo PO as for group 1 (1603); placebo PO as for group 2 (888) E: placebo PO (575) F: placebo (saline) IV (194); timing not specified G: no treatment (71) H: placebo (saline) IV (149) I: placebo (saline) IV (116)	End-point of follow-up: Not reported For how many participants were no complete outcome data available? Not reported	Outcome measure-1 No reports on death, cardiopulmonary resuscitation, irreversible neurological deficit, or prolonged hospital stays were found. In two trials, 3/778 (0.4%) patients who received oral methylprednisolone 2×32 mg or intravenous prednisolone 250 mg had laryngeal oedema compared with 11/769 (1.4%) controls (odds ratio 0.31, 95% confidence interval 0.11 to 0.88). In two trials, 7/3093 (0.2%) patients who received oral methylprednisolone 2×32 mg had a composite outcome (including shock, bronchospasm, and laryngospasm) compared with 20/2178 (0.9%) controls (odds ratio 0.28, 0.13 to 0.60). In one trial, 1/196 (0.5%) patients who received intravenous clemastine 0.03 mg/kg and cimetidine 2-5 mg/kg had	Facultative: Brief description of author's conclusion: Life threatening anaphylactic reactions due to iodinated contrast media are rare. In unselected patients, the usefulness of premedication is doubtful, as a large number of patients need to receive premedication to prevent one potentially serious reaction. Data supporting the use of premedication in patients with a history of allergic reactions are lacking. Physicians who are dealing with these patients should not rely on the efficacy of premedication. Level of evidence: GRADE Very Low due to high risk of bias (problems with allocation and blinding) and imprecision (small amount of events, very rare serious adverse events)

		included <u>Important patient characteristics at baseline</u>: *Number of patients; characteristics important to the research question and/or for statistical adjustment (confounding in cohort studies); for example, age, sex, bmi, ...* <u>N, mean age</u> A: 400 patients, age NR B: 121 patients, age NR C: 86 patients, age NR D: 6763 patients, age NR E: 1155 patients, age NR F: 779 patients, age NR G: 220 patients, age NR	H: Dimenhydrinate 25 mg IV 15 to 45 min before (150); I: Clemastine 2 mg IV with CM (92);			angio-oedema compared with 8/194 (4.1%) controls (odds ratio 0.20, 0.05 to 0.76).	

		H: 299 patients, age NR I: 208 patients, age NR *Sex:* NR Groups comparable at baseline? Unclear					

Table of quality assessment - prognostic factor (PF) studies

Based on: QUIPS[A] (Haydn, 2006; Haydn 2013)

Research question:

Study reference **(first author, year of publication)**	**Study participation[1]** **Study sample represents the population of interest on key characteristics?** **(high/moderate/low risk of selection bias)**	**Study Attrition[2]** **Loss to follow-up not associated with key characteristics (i.e., the study data adequately represent the sample)?** **(high/moderate/low risk of attrition bias)**	**Prognostic factor measurement[3]** **Was the PF of interest defined and adequately measured?** **(high/moderate/low risk of measurement bias related to PF)**	**Outcome measurement[3]** **Was the outcome of interest defined and adequately measured?** **(high/moderate/low risk of measurement bias related to outcome)**	**Study confounding[4]** **Important potential confounders are appropriately accounted for?** **(high/moderate/low risk of bias due to confounding)**	**Statistical Analysis and Reporting[5]** **Statistical analysis appropriate for the design of the study?** **(high/moderate/low risk of bias due to statistical analysis)**
Chen, 2015	Low	Low	Low	Low	Low	Low
Jung, 2016	Low	Low	Low	Low	Low	Low
Park, 2017	Low	Low	Low	Low	Low	Low

[A] https://methods.cochrane.org/sites/methods.cochrane.org.prognosis/files/public/uploads/QUIPS%20tool.pdf

[1] Adequate description of: source population or population of interest, sampling and recruitment, period and place of recruitment, in- and exclusion criteria, study participation, and baseline characteristics.

[2] Adequate response rate, information on dropouts and loss to follow-up, no differences between participants who completed the study and those lost to follow-up.

[3] Method of measurement is valid, reliable, setting of measurement is the same for all participants.

[4] Important confounders are listed, method of measurement is valid, reliable, setting of measurement is the same for all participants, important confounders are accounted for in the design (matching, stratification, initial assembly of comparable groups), or analysis (appropriate adjustment)

[5] Enough data are presented to assess adequacy of the analysis, strategy of model building is appropriate and based on conceptual framework, no selective reporting

Evidence table for prognostic factor studies

Research question:

Study reference	Study characteristics	Patient characteristics	Prognostic factor(s)	Follow-up	Estimates of prognostic effect	Comments
Chen, 2015	Type of study: observational Setting and country: China Funding and conflicts of interest: first author is an employee of Bayer HealthCare. The other authors have no conflicts of interest to disclose.	Inclusion criteria: Patients undergoing cardiac catheterization were enrolled. Exclusion criteria: Pregnant and lactating women, and patients who had contraindications towards iopromide or towards cardiac catheterization, were excluded. N=17513 Mean age ± SD: 60 ± 11 years Sex: 66% M / 34% F	Describe prognostic factor(s) and method of measurement: Not described explicitly, but described in results section (see column Outcomes).	Duration or endpoint of follow-up: Unclear For how many participants were no complete outcome data available? Not reported Reasons for incomplete outcome data described? Not reported	that acute adverse drug reactions (ADRs) occurred in 66/17,513 (0.38%) patients undergoing iopromide (300 or 370 mgI/mL) administration during coronary angiography or Percutaneous Coronary Intervention (PCI), out of which 2 ADRs (0.01%) were severe. Most ADRs manifested as nausea vomiting (0.22%) and rash (0.09%). The following factors were associated with risk of ADR: age 50-69 versus age < 50 (OR: 0.48, 95% CI: 0.27 to 0.85); premedication with corticosteroids (OR: 0.41, 95% CI: 0.18 to 0.97); contrast dose ≥100mL (OR 0.50, 95% CI 0.30 to 0.82); pre-procedural hydration (OR: 0.11, 95% CI: 0.04 to 0.33); left main coronary disease (OR: 2.27, 95% CI: 1.15 to 4.48); previous ADR to contrast (OR: 9.30, 95% CI: 1.10 to78.84). Allergic constitution, asthma and sex were not independently associated with the risk of developing an adverse reaction.	Adverse events (AEs) were recorded by the investigator in a case report form (CRF). The incidence, seriousness, duration, relationship to study drug, action taken and outcome were recorded. AEs were judged to be ADRs (i.e. related to study drug) by either the investigator and by the study sponsor, Bayer HealthCare Company Ltd.
Jung,	Type of study:	Inclusion criteria: high-risk	Describe prognostic factor(s) and	Duration or	47/322 (15%) of the patients	

2016	retrospective observational Setting and country: Korea, hospital Funding and conflicts of interest: not reported	patients, defined as those who had a previous history of acute allergic-like reactions to LOCM, underwent CT enhanced with LOCM after premedication at Seoul National University Hospital between June 2010 and May 2012. Exclusion criteria: not reported N= 322 Mean age ± SD: 55 ± 13 Sex: 47% M / 53% F	method of measurement: Patient demographics, comorbid diseases, and prescription medications taken at the time the patients underwent CT were extracted from electronic medical records. A retrospective review of the following information was performed: nature and severity of previous reactions, recurrence of hypersensitivity after premedication, interval between ICM exposures, and the details of the premedication regimen.	endpoint of follow-up: For how many participants were no complete outcome data available? Not reported Reasons for incomplete outcome data described? Not reported	experienced a recurrence of an allergic reaction after low-osmolality iodinated contrast medium administration for computed tomography, despite premedication. The following factors were associated with an increased risk for developing this second acute allergic-like adverse reaction: age (OR: 0.97, 95% CI: 0.94 to 0.99);previous severe reaction (OR: 8.88, 95% CI: 2.11 to 37.42); corticosteroid premedication (OR: 0.28, 95% CI: 0.10 to 0.78). The following factors were not independently associated with the risk of acute allergic-like adverse reactions: sex, bronchial asthma, allergic rhinitis, chronic urticaria, food allergy, other drug allergy, H2-antihistamines premedication.	
Park, 2017	Type of study: retrospective observational Setting and country: Korea, hospital Funding and conflicts of interest: not reported	Inclusion criteria: all patients who had previously experienced a moderate or severe initial HSR to LOCM and in whom the subsequent exposure occurred between 1 January 2014 and 31 December 2014. Exclusion criteria: not reported	Describe prognostic factor(s) and method of measurement: Not described explicitly, but described in results section (see column Outcomes).	Duration or endpoint of follow-up: For how many participants were no complete outcome data available? N (%): not reported	recurrence of hypersensitivity reactions after contrast exposure occurred in 64/328 (20%) of the instances of re-exposure to low-osmolar iodinated contrast in patients with a history of moderate or severe reactions. The following factors were associated with an increased risk for developing this second hypersensitivity reaction: age (OR: 0.97, 95% CI 0.94 to 0.99);	

		N=150 Mean age ± SD: 62 ± 12 Sex: 50 % M / 50 % F		Reasons for incomplete outcome data described? Not reported	diabetes mellitus (OR: 6.49, 95% CI: 2.38 to 17.71); chronic urticaria (OR: 7.61, 95% CI: 1.63 to 35.59); drug allergy (OR: 3.69, 95% CI: 1.18 to 11.56); changing the iodinated contrast medium (OR: 0.33, 95% CI: 0.17 to 0.64); initial hypersensitivity reaction was severe (OR: 2.67, 95% CI: 1.05 to 6.79). The following factors were not independently associated with the risk of developing a recurrent hypersensitivity reaction: sex, use of premedication.	

[1] Incremental predictive value is the predictive value beyond standard demographic factors and the established risk factors (e.g. smoking, blood pressure, lipid levels, diabetes, cancer stage, et cetera), for example change in c-statistic.

Exclusion tables

Table: exclusion after examination of the full text

Author and Year	Reason for exclusion
Agardth, 1983	Does not fulfil inclusion criteria: no control group.
Aggarwal, 2015	Does not fulfil inclusion criteria: the effect of prophylactic measures is not examined (this is a sefty study on the risks of beta-blockers).
Ahn, 2015	Does not fulfil inclusion criteria: the diagnostic criteria of cutaneous test for hypersensitivity reactions after contrast administration are studied.
Al-Ahmad, 2015	Two case-reports.
Ansell, 1980	Does not fulfil inclusion criteria: univariate analysis of risk factor of hypersensitivity reactions after contrast administration only.
Aurnol, 2013	Conference abstract
Barrett, 1992	Does not fulfil inclusion criteria: hypersensitivity reactions are not reported as an outcome
Beaty, 2008	Does not fulfil inclusion criteria: examines physician's beliefs about the relation between contrast hypersensitivity and seafood allergy.
Bellin, 2011	Narrative review
Ben-Noun, 1998	Does not fulfil inclusion criteria: descirbes relation between drug-induced asthma and contrast medium
Benson, 2017	Does not fulfil inclusion criteria: describes result of hospital alert system, no control group.
Berti, 2016	Does not fulfil inclusion criteria: describes diagnostic properties of cutaneous tests for contrast medium for hypersensitivity reactions
Bertrand, 1992	Already included in systematic review of Tramer, 2006
Boehm, 2016	Narrative review
Bohm, 2006	Narrative review
Bohm, 2012	Does not fulfil inclusion criteria: proposes a classification system for hypersensitivity reaction, no original patient data presented
Bohm, 2017	Does not fulfil inclusion criteria: article is in German
Bonadonna, 2014	Narrative review
Bottinor, 2013	Narrative review
Boulos, 2017	Does not fulfil inclusion criteria: validation of a sepsis prediction score
Boyd, 2017	Narrative review
Brockow, 2005	Narrative review
Brockow, 2014	Narrative review
Bumbacea, 2013	Narrative review
Chevrot, 1988	Already included in systematic review of Tramer, 2006
Choi, 2008	Case-report
Christiansen, 2002	Narrative review
Chuang, 2009	Does not fulfil inclusion criteria: contrast hypersensitivity is not an outcome measure
Cohan, 1997	Narrative review
Courvoisier, 1998	Case report
Davenport, 2009	Does not fulfil inclusion criteria: univariate analysis of risk factor of hypersensitivity reactions after contrast administration only.
Davenport, 2010	Does not fulfil inclusion criteria: studies saftey of a corticosteroid regimen
Davenport, 2011	Does not fulfil inclusion criteria: studies saftey of a corticosteroid regimen
Davenport, 2016	Does not fulfil inclusion criteria: studies saftey of a corticosteroid regimen
Davenport, 2017	Narrative review
Davis, 2015	Narrative review
Della-Torre, 2015	Does not fulfil inclusion criteria: no control group
Dewachter, 2011	Does not fulfil inclusion criteria: effect of preventive measures not examined
Dillman, 2007	Does not fulfil inclusion criteria: effect of preventive measures not examined
Dillman, 2008	Does not fulfil inclusion criteria: univariate analysis of risk factor of hypersensitivity reactions after contrast administration only.
Engl, 1988	Letter tot he Editor
Esplugas, 2002	Narrative review
Farnam, 2012	Narrative review
Fineman, 2014	Narrative review
Freed, 2001	Does not fulfil inclusion criteria: univariate analysis of risk factor of hypersensitivity reactions after contrast administration only.
Ginsberg, 1996	Already included in systematic review of Tramer, 2006
Gomes, 2005	Narrative review
Hermans, 2017	Narrative review

Heshmatzadeh, 2016	Narrative review
Hsieh, 2014	Does not fulfil inclusion criteria: studies the effects of ignoring drug allergy alerts in electronic patient database
Hsu Blatman, 2017	Narrative review
Inbaraj, 1970	Narrative review or book chapter
Inbaraj, 2017	Does not fulfil inclusion criteria: no univariate or multivariate analysis of risk factor of hypersensitivity reactions after contrast administration.
Jingu, 2014	Does not fulfil inclusion criteria: no univariate or multivariate analysis of risk factor of hypersensitivity reactions after contrast administration.
Kalaiselvan, 2014	Does not fulfil inclusion criteria: univariate analysis of risk factor of hypersensitivity reactions after contrast administration only.
Kaufman, 2013	Does not fulfil inclusion criteria: adresses medical myths in narrative review.
Ketkar, 2003	Case report
Kim, 2011	Does not fulfil inclusion criteria: no control group
Kopp, 2008	Does not fulfil inclusion criteria: univariate analysis of risk factor of hypersensitivity reactions after contrast administration only.
Kwan, 2006	Does not fulfil inclusion criteria: univariate analysis of risk factor of hypersensitivity reactions after contrast administration only.
Kyung, 2013	Does not fulfil inclusion criteria: analysis of classification systems for hypersensitivity reactions after contrast administration only.
Ioh, 2010	Does not fulfil inclusion criteria: no univariate or multivariate analysis of risk factor of hypersensitivity reactions after contrast administration.
Lasser, 1987	Already included in systematic review of Tramer, 2006
Lasser, 1988	Same population and results as Lasser, 1987 (which is included in the literature analysis).
Lasser, 1994	Already included in systematic review of Tramer, 2006
Lasser, 1995	Letter to the editor
Lasser, 2004	Narrative review
Lee, 2017	Does not fulfil inclusion criteria: no control group
Leone, 2008	Does not fulfil inclusion criteria: describes causes of adverse drug reactions overall
Liccardi, 2008	Narrative review
Liccardi, 2009	Narrative review
Mammarappallil, 2016	Does not fulfil inclusion criteria: report show often adverse reactions after contrast administration are not documenten adrquately
Marcelino, 2016	Conference abstract
Maurer, 2013	Conference abstract
Mervak, 2015	Does not fulfil inclusion criteria: univariate analysis of risk factor of hypersensitivity reactions after contrast administration only.
Mervak, 2016	Conference abstract
Mishra, 2013	Does not fulfil inclusion criteria: univariate analysis of risk factor of hypersensitivity reactions after contrast administration only.
Montandon, 2016	Two case-reports
Morcos, 1998	Letter to the editor
Morcos, 2005	Narrative review
Morzycki, 2017	Narrative review
Muller, 2014	Does not fulfil inclusion criteria: no univariate or multivariate analysis of risk factor of hypersensitivity reactions after contrast administration.
Nazer, 2011	Conference abstract
Newman, 2001	Case report
Nguyen, 2008	Does not fulfil inclusion criteria: contrast hypersensitivity is not an outcome measure
Niell, 2014	Does not fulfil inclusion criteria: studies the educational value of an online didactic model about contrast hypersensitivity reactions
Nilsson, 2001	Does not fulfil inclusion criteria: no control group of patients with a history of hypersensitivity to contrast medium, who do not receive prophylactic measures
Petscavge, 2014	Does not fulfil inclusion criteria: studies the educational value of an didactic tool about contrast hypersensitivity reactions
Plagova, 2017	Narrative review
Power, 2016	Does not fulfil inclusion criteria: univariate analysis of risk factor of hypersensitivity reactions after contrast administration only.
Pradubpongsa, 2013	Does not fulfil inclusion criteria: univariate analysis of risk factor of hypersensitivity reactions after contrast administration only.

Prieto-Garcia, 2013	Does not fulfil inclusion criteria: examines diagnostic properties of cutaneous tests for diagnosing hypersensitivity reactions after contrast administration.
Rajesh, 2016	Conference abstract
Rerkpattanapipat, 2011	Narrative review
Ring, 1985	Already included in systematic review of Tramer, 2006
Rosada Ingelmo, 2016	Narrative review
Ryu, 2015	Does not fulfil inclusion criteria: univariate analysis of risk factor of hypersensitivity reactions after contrast administration only.
Schopp, 2013	Narrative review
Seymour, 1994	Does not fulfil inclusion criteria: descirbes practice variation in administration of prophylaxis for hypersensitivity reactions after contrast administration.
Seymour, 1995	Letter to the Editor
Sheikh, 2013	Narrative review
Siegrist, 2016	Case report
Sikka, 2016	Narrative review
Simons, 2010	Narrative review
Small, 1982	Already included in systematic review of Tramer, 2006
Smithe, 1995	Already included in systematic review of Tramer, 2006
Soffer, 2017	Case report
Soyyigit, 2016	Does not fulfil inclusion criteria: examines diagnostic properties of cutaneous tests for diagnosing hypersensitivity reactions after contrast administration.
Szebeni, 2001	Narrative review
Szebeni, 2005	Narrative review
Tepetam, 2016	Does not fulfil inclusion criteria: univariate analysis of risk factor of hypersensitivity reactions after contrast administration only.
Trcka, 2008	Does not fulfil inclusion criteria: examines diagnostic properties of cutaneous tests for diagnosing hypersensitivity reactions after contrast administration.
Trout, 2011	Does not fulfil inclusion criteria: physician survey on use of gadolinium containing contrast medium in children.
Tsushima, 2016	Does not fulfil inclusion criteria: physician survey on knowledge of risk factors of complications of contrast medium administration.
Wang, 2008	Does not fulfil inclusion criteria: univariate analysis of risk factor of hypersensitivity reactions after contrast administration only.
Wang, 2017	Does not fulfil inclusion criteria: describes the use of epinephrine for all drug hypersensitivity reactions
Wu, 2016	Commenatry, not an original article.
Yang, 2015	Does not fulfil inclusion criteria: describes the before and after effects of an electrocin consultation system on the risk of of hypersensitivity reactions after contrast administration.
Zukiwski, 1990	Does not fulfil inclusion criteria: describes risk factors in a very specific population, univariate analysis only.

Search strategy

Database	Search string	Total
PubMed 1980 – december 2017	(("Contrast Media"[Mesh] OR contrast medi* [tiab] OR contrast agent* [tiab] OR contrast material* [tiab] OR radiocontrast medi* [tiab] OR radiocontrast agent* [tiab] OR radiopaque medi* [tiab] OR "Barium"[Mesh] OR barium [tiab]) AND (("Antibiotic Prophylaxis"[Mesh] OR prophylax* [tiab] OR prevent* [tiab] OR premedicat* [tiab] OR pretreatment [tiab] OR breakthrough reaction* [tiab] OR "Drug Hypersensitivity/therapy"[Mesh]) AND (hypersensitiv* [tiab] OR allergic* [tiab] OR anaphylact* [tiab] OR adverse reaction*[tiab] OR immediate generalized [tiab] OR corticosteroid* [tiab] OR antihistamin* [tiab]))) AND ("1980"[Date - Publication] : "3000"[Date - Publication]) AND "english"[Language] = 341	478
Embase (Elsevier)	('contrast medium'/exp OR (((contrast OR radiocontrast) NEAR/2 (medi* OR agent* OR material*)):ab,ti) OR 'radiopaque medi*':ab,ti OR 'barium'/exp OR barium:ab,ti) AND (('prophylaxis'/exp OR prophylax*:ab,ti OR prevent*:ab,ti OR premedicat*:ab,ti OR pretreatment:ab,ti OR 'breakthrough reaction*':ab,ti OR 'drug hypersensitivity'/exp/dm_th) AND ('hypersensitivity'/exp OR hypersensitiv*:ab,ti OR allergic*:ab,ti OR anaphylact*:ab,ti OR 'adverse reaction*':ab,ti OR 'immediate generalized':ab,ti OR corticosteroid*:ab,ti OR antihistamin*:ab,ti))	

	AND [english]/lim AND [1980-2018]/py *Gebruikte filters:* *Systematische reviews:* ('meta analysis'/de OR cochrane:ab OR embase:ab OR psycinfo:ab OR cinahl:ab OR medline:ab OR ((systematic NEAR/1 (review OR overview)):ab,ti) OR ((meta NEAR/1 analy*):ab,ti) OR metaanalys*:ab,ti OR 'data extraction':ab OR cochrane:jt OR 'systematic review'/de) NOT (('animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp) *RCT's:* ('clinical trial'/exp OR 'randomization'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp OR 'placebo'/exp OR 'prospective study'/exp OR rct:ab,ti OR random*:ab,ti OR 'single blind':ab,ti OR 'randomised controlled trial':ab,ti OR 'randomized controlled trial'/exp OR placebo*:ab,ti) NOT 'conference abstract':it *Observationeel onderzoek:* 'clinical study'/de OR 'case control study'/de OR 'family study'/de OR 'longitudinal study'/de OR 'retrospective study'/de OR ('prospective study'/de NOT 'randomized controlled trial'/de) OR 'cohort analysis'/de OR ((cohort NEAR/1 (study OR studies)):ab,ti) OR (case:ab,ti AND ((control NEAR/1 (study OR studies)):ab,ti)) OR (follow:ab,ti AND ((up NEAR/1 (study OR studies)):ab,ti)) OR ((observational NEAR/1 (study OR studies)):ab,ti) OR ((epidemiologic NEAR/1 (study OR studies)):ab,ti) OR (('cross sectional' NEAR/1 (study OR studies)):ab,ti) = 212	

Appendices to module 6

Knowledge gaps

The incidence of PC-AKI after administration of GBCA is unknown.

The difference in nephrotoxic potential between different GBCA's is unknown.

Indicators

None.

Implementation

Recommendation	Time frame for implementation: <1 year, 1 to 3 years or >3 years	Expected effect on costs	Limitations for implementation	Barriers to implementation[1]	Actions needed for implementation[2]	Parties responsible for actions[3]	Other remarks
Use the lowest dose GBCA needed to achieve a diagnostic MRI examination.	1 to 3 years	None	Lack of knowledge of guideline	Lack of knowledge of guideline	Dissemination of guideline	NVvR	
Do not use prophylactic measures to avoid the development of PC-AKI in high risk patients (eGFR<30ml/min/1.73m^2) receiving GBCA intravenously at the appropriate dose.	1 to 3 years	None	Lack of knowledge of guideline	Lack of knowledge of guideline	Dissemination of guideline	NVvR	
Do not substitute ICM with GBCA in order to avoid PC-AKI in computed tomography and/or digital subtraction angiography.	1 to 3 years	None	Lack of knowledge of guideline	Lack of knowledge of guideline	Dissemination of guideline	NVvR	

[1] Barriers can be found at multiple levels. They can exist at the level of the consultant, the hospital organisation, and the health care system.
[2] Actions needed for implementation, but also actions to promote implementation. Think about checks during quality visits, guideline publication, information of hospital management, et cetera.
[3] Who is responsible for implementation of recommendations will largely be determined by the level where the barriers are expected to be.

Exclusion table

Table of Exclusions after reading full text

Author and Year	Reason of exclusion
Belling 2002	Does not fulfil selection criteria. No control group. Descriptive.
Cochran 2002	Does not fulfil selection criteria. No control group. Descriptive.
Cohan 1997	Does not fulfil selection criteria. No control group. Descriptive.
Conner 2017	Does not fulfil selection criteria. No control group. Descriptive.
Conner 2017	Does not fulfil selection criteria. No control group. Descriptive.
Davenport 2012	Does not fulfil selection criteria. No control group. Descriptive.
Ding 2018	Does not discuss treatment of extravasation
Ding 2018	Does not fulfil selection criteria. No control group. Descriptive.
Earhart 2011	Does not fulfil selection criteria. No control group. Descriptive.

Fallscheer 2007	Does not fulfil selection criteria. No control group. Descriptive.
Kim 2017	Does not fulfil selection criteria. No control group. Descriptive.
Kim 2017	Does not fulfil selection criteria. No control group. Descriptive.
Nicola 2016	Does not fulfil selection criteria. No control group. Descriptive.
Rose 2015	Does not fulfil selection criteria. No control group. Descriptive.
Sbitany 2010	Does not fulfil selection criteria. No control group. Descriptive.
Schaverien 2008	Does not fulfil selection criteria. No control group. Descriptive.
Schummer 2010	Does not fulfil selection criteria. No control group. Descriptive.
Sonis 2017	Does not fulfil selection criteria. No control group. Descriptive.
Sonis 2017	Does not fulfil selection criteria. No control group. Descriptive.
Sum 2006	Does not fulfil selection criteria. No control group. Descriptive.
Tonolini 2012	Does not fulfil selection criteria. No control group. Descriptive.
Tonolini 2016	No comparison therapies. Letter tot the editor on the occasion of Nicola 2016
Tsai 2007	Does not fulfil selection criteria. No control group. Descriptive.
Vandeweyer 2000	Does not fulfil selection criteria. No control group. Descriptive.
Wang 2007	Does not fulfil selection criteria. No control group. Descriptive.
Wilson 2011	Does not fulfil selection criteria. No control group. Descriptive.

Search strategy

Database	Search terms	Total
PubMed 1996 – februari 2018	(("Extravasation of Diagnostic and Therapeutic Materials"[Mesh] OR extravasation* [tiab] OR compartment syndrome*[tiab]) AND ("Contrast Media"[Majr] OR contrast medi*[ti])) AND (("1996/01/01"[PDat] : "3000/12/31"[PDat]) AND (English[lang] OR Dutch[lang])) *Systematic Review filter:* (systematic*[tiab] AND (bibliographic*[TIAB] OR literature[tiab] OR review[tiab] OR reviewed[tiab] OR reviews[tiab])) OR (comprehensive*[TIAB] AND (bibliographic*[TIAB] OR literature[tiab])) OR "cochrane database syst rev"[Journal] OR "Evidence report/technology assessment (Summary)"[journal] OR "Evidence report/technology assessment"[journal] OR "integrative literature review"[tiab] OR "integrative research review"[tiab] OR "integrative review"[tiab] OR "research synthesis"[tiab] OR "research integration"[tiab] OR cinahl[tiab] OR embase[tiab] OR medline[tiab] OR psyclit[tiab] OR (psycinfo[tiab] NOT "psycinfo database"[tiab]) OR pubmed[tiab] OR scopus[tiab] OR "web of science"[tiab] OR "data synthesis"[tiab] OR meta-analys*[tiab] OR meta-analyz*[tiab] OR meta-analyt*[tiab] OR metaanalys*[tiab] OR metaanalyz*[tiab] OR metaanalyt*[tiab] OR "meta-analysis as topic"[MeSH:noexp] OR Meta-Analysis[ptyp] OR ((review[tiab] AND (rationale[tiab] OR evidence[tiab])) AND review[pt]) *RCT filter:* ((random*[tiab] AND (controlled[tiab] OR control[tiab] OR placebo[tiab] OR versus[tiab] OR versus[tiab] OR group[tiab] OR groups[tiab] OR comparison[tiab] OR compared[tiab] OR arm[tiab] OR arms[tiab] OR crossover[tiab] OR cross-over[tiab]) AND (trial[tiab] OR study[tiab])) OR ((single[tiab] OR double[tiab] OR triple[tiab]) AND (masked[tiab] OR blind*[tiab]))) OR ((random*[ot] AND (controlled[ot] OR control[ot] OR placebo[ot] OR versus[ot] OR versus[ot] OR group[ot] OR groups[ot] OR comparison[ot] OR compared[ot] OR arm[ot] OR arms[ot] OR crossover[ot] OR cross-over[ot]) AND (trial[ot] OR study[ot])) OR ((single[ot] OR double[ot] OR triple[ot]) AND (masked[ot] OR blind*[ot]))) = 319	480
Embase (Elsevier)	(('extravasation'/exp OR extravasation*:ab,ti OR 'compartment syndrom*':ab,ti) AND ('contrast medium'/exp/mj OR 'contrast medi*':ti) AND ([dutch]/lim OR [english]/lim) AND [1996-2018]/py) NOT 'conference abstract':it)) *Systematic Review filter*: (('meta analysis'/de OR cochrane:ab OR embase:ab OR psycinfo:ab OR cinahl:ab OR medline:ab OR	

	((systematic NEAR/1 (review OR overview)):ab,ti) OR ((meta NEAR/1 analy*):ab,ti) OR metaanalys*:ab,ti OR 'data extraction':ab OR cochrane:jt OR 'systematic review'/de) NOT (('animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp))) *RCT filter*: (('clinical trial'/exp OR 'randomization'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp OR 'placebo'/exp OR 'prospective study'/exp OR rct:ab,ti OR random*:ab,ti OR 'single blind':ab,ti OR 'randomised controlled trial':ab,ti OR 'randomized controlled trial'/exp OR placebo*:ab,ti) NOT 'conference abstract':it)) = 319	

Appendices to module 7

Knowledge Gaps

It is unclear whether ionic macrocyclic GBCAs compared to non-ionic macrocyclic GBCAs in renal insufficiency patients (eGFR <30 ml/min/1.73m^2) are associated with different risk of NSF.

It is unclear whether residual kidney function in dialysis patients is effected by the timing of haemodialysis after administration of GBCA.

It is unclear whether timing of dialysis after administration of GBCA affects patient outcomes.

Quality Assurance Indicators

None.

Implementation of Recommendations

Recommendation	Time frame for implementation: <1 year, 1-years or >3 years	Expected effect on costs	Limitations for implementation	Barriers to implementation[1]	Actions needed for implementation[2]	Responsible for actions[3]	Other remarks
Make an individual risk-benefit analysis with the patient's requesting physician and nephrologist to ensure a strict indication for gadolinium-enhanced MRI in patients with eGFR < 30 ml/min/1.73m^2.	1 to 3 years	None	Lack of knowledge of guideline	Lack of knowledge of guideline	Dissemination of guideline	NVvR	
For optimal prevention of NSF in patients with eGFR < 30 ml/min/1.73m^2 use low-risk (ionic and non-ionic) macrocyclic GBCAs for medical imaging.	1 to 3 years	None	Lack of knowledge of guideline	Lack of knowledge of guideline	Dissemination of guideline	NVvR	
In patients on chronic haemodialysis, GBCA administration may electively be scheduled shortly before the next haemodialysis session to limit	1 to 3 years	None	Lack of knowledge of guideline	Lack of knowledge of guideline	Dissemination of guideline	NVvR	

the amount of circulating GBCA.							
For prevention of NSF in patients who are already dependent on haemodialysis or peritoneal dialysis, the administration of GBCA does not have to be followed by an immediate haemodialysis session.	1 to 3 years	None	Lack of knowledge of guideline	Lack of knowledge of guideline	Dissemination of guideline	NVvR	

[1] Barriers can be found at multiple levels. They can exist at the level of the consultant, the hospital organisation, and the health care system.

[2] Actions needed for implementation, but also actions to promote implementations. Think about checks during quality visits, guideline publication, information of hospital management, et cetera.

[3] Who is responsible for implementation of recommendations will largely be determined by the level where the barriers are expected to be.

Exclusion Table

After full text review

Author, year	Reason for exclusion
Agarwal 2009	Does not fulfil PICO criteria: no prognostic factors included
Bahrami 2009	Does not fulfil selection criteria: no multivariate analysis (univariate)
Bernstein 2014	Does not fulfil selection criteria: no multivariate analysis (univariate)
Bruce 2016	Does not fulfil selection criteria: no multivariate analysis
Deray 2014	Does not fulfil PICO criteria: no prognostic factors included
Elmholdt 2011	Does not fulfil selection criteria: no multivariate analysis (univariate)
Lauenstein 2015	Does not fulfil PICO criteria: no prognostic factors included
Marckmann 2007	Does not fulfil selection criteria: no multivariate analysis (univariate)
Martin 2010	Does not fulfil selection criteria: no multivariate analysis
Mazhar 2009	Does not fulfil selection criteria: no multivariate analysis (descriptive statistics)
Michaely 2017	Does not fulfil selection criteria: no multivariate analysis (descriptive statistics)
Nacif 2012	Does not fulfil PICO criteria: no prognostic factors included
Othersen 2007	Does not fulfil selection criteria: no multivariate analysis (descriptive statistics)
Rydahl 2008	Does not fulfil selection criteria: no multivariate analysis (descriptive statistics)
Soulez 2015	Does not fulfil selection criteria: no multivariate analysis (descriptive statistics)
Todd 2007	Does not fulfil PICO criteria: no prognostic factors NSF included
Wang 2011	Does not fulfil selection criteria: no multivariate analysis (univariate)
Zhang 2015	Does not fulfil PICO criteria: no rognostic factors included

Literature Search research question 7a

Database	Search String	Total
PubMed 2000 – February 2018	(('contrast medium'/exp OR 'contrast medi*':ti,ab OR 'contrast agent*':ti,ab OR 'contrast material*':ti,ab OR 'contrast induced':ti,ab OR 'contrast related':ti,ab OR 'contrast exposure':ti,ab OR 'contrast dosage':ti,ab OR 'contrast dose*':ti,ab OR 'contrast enhanced':ti,ab OR 'contrast administration':ti,ab OR 'gadolinium'/exp OR gadolinium*:ti,ab OR gbca*:ti,ab OR primovist:ti,ab OR eovist:ti,ab OR omniscan:ti,ab OR magnevist:ti,ab OR optimark:ti,ab OR prohance:ti,ab OR multihance:ti,ab OR dotarem:ti,ab OR gadovist:ti,ab OR gadodiamide:ti,ab OR gadopentetat*:ti,ab OR gadoversetamide:ti,ab OR gadoteridol:ti,ab OR gadobenate:ti,ab OR gadoterate:ti,ab OR	228

	'gadofosveset trisodium':ti,ab OR gadobutrol:ti,ab OR 'gadoxetic acid':ti,ab OR 'gadoxetate disodium':ti,ab OR 'gd dtpa':ti,ab OR 'gd hp do3a':ti,ab OR 'gd dtpa bma':ti,ab OR 'gd dota':ti,ab OR 'gd dtpa bmea':ti,ab OR 'gd bopta':ti,ab OR 'gd bt do3a':ti,ab OR 'gd eob dtpa':ti,ab OR meglumine:ti,ab OR dimeglumine:ti,ab OR 'ultrasound contrast agent*':ti,ab OR 'us contrast agent*':ti,ab OR 'ultrasound contrast medi*':ti,ab OR sonovue:ti,ab OR optison:ti,ab OR perflutren:ti,ab OR hexafluoride:ti,ab OR 'barium'/exp OR barium:ti,ab OR micropaque:ti,ab OR 'e z cat':ti,ab OR polibar:ti,ab OR barite:ti,ab OR baritop:ti,ab) AND ('nephrogenic systemic fibrosis'/exp/mj OR 'nephrogenic systemic fibros*':ti OR nsf:ti OR 'nephrogenic fibrosing dermopath*':ti OR nfd:ti)) AND ([dutch]/lim OR [english]/lim) NOT [conference abstract]/lim AND [2000-2018]/py Filter SR: ('meta analysis'/de OR cochrane:ab OR embase:ab OR psycinfo:ab OR cinahl:ab OR medline:ab OR ((systematic NEAR/1 (review OR overview)):ab,ti) OR ((meta NEAR/1 analy*):ab,ti) OR metaanalys*:ab,ti OR 'data extraction':ab OR cochrane:jt OR 'systematic review'/de) NOT (('animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp) = 11 Filter RCT: ((random*[tiab] AND (controlled[tiab] OR control[tiab] OR placebo[tiab] OR versus[tiab] OR versus[tiab] OR group[tiab] OR groups[tiab] OR comparison[tiab] OR compared[tiab] OR arm[tiab] OR arms[tiab] OR crossover[tiab] OR cross-over[tiab]) AND (trial[tiab] OR study[tiab])) OR ((single[tiab] OR double[tiab] OR triple[tiab]) AND (masked[tiab] OR blind*[tiab]))) OR ((random*[ot] AND (controlled[ot] OR control[ot] OR placebo[ot] OR versus[ot] OR versus[ot] OR group[ot] OR groups[ot] OR comparison[ot] OR compared[ot] OR arm[ot] OR arms[ot] OR crossover[ot] OR cross-over[ot]) AND (trial[ot] OR study[ot])) OR ((single[ot] OR double[ot] OR triple[ot]) AND (masked[ot] OR blind*[ot]))) = 7 Filter observationele studies: "cohort studies"[mesh] OR "case-control studies"[mesh] OR "comparative study"[pt] OR "risk factors"[mesh] OR "cohort"[tw] OR "compared"[tw] OR "groups"[tw] OR "case control"[tw] OR "multivariate"[tw] = 205 = 211 uniek	
Embase (Elsevier)	(('contrast medium'/exp OR 'contrast medi*':ti,ab OR 'contrast agent*':ti,ab OR 'contrast material*':ti,ab OR 'contrast induced':ti,ab OR 'contrast related':ti,ab OR 'contrast exposure':ti,ab OR 'contrast dosage':ti,ab OR 'contrast dose*':ti,ab OR 'contrast enhanced':ti,ab OR 'contrast administration':ti,ab OR 'gadolinium'/exp OR gadolinium*:ti,ab OR gbca*:ti,ab OR primovist:ti,ab OR eovist:ti,ab OR omniscan:ti,ab OR magnevist:ti,ab OR optimark:ti,ab OR prohance:ti,ab OR multihance:ti,ab OR dotarem:ti,ab OR gadovist:ti,ab OR gadodiamide:ti,ab OR gadopentetat*:ti,ab OR gadoversetamide:ti,ab OR gadoteridol:ti,ab OR gadobenate:ti,ab OR gadoterate:ti,ab OR 'gadofosveset trisodium':ti,ab OR gadobutrol:ti,ab OR 'gadoxetic acid':ti,ab OR 'gadoxetate disodium':ti,ab OR 'gd dtpa':ti,ab OR 'gd hp do3a':ti,ab OR 'gd dtpa bma':ti,ab OR 'gd dota':ti,ab OR 'gd dtpa bmea':ti,ab OR 'gd bopta':ti,ab OR 'gd bt do3a':ti,ab OR 'gd eob dtpa':ti,ab OR meglumine:ti,ab OR dimeglumine:ti,ab OR 'ultrasound contrast agent*':ti,ab OR 'us contrast agent*':ti,ab OR 'ultrasound contrast medi*':ti,ab OR sonovue:ti,ab OR optison:ti,ab OR perflutren:ti,ab OR hexafluoride:ti,ab OR 'barium'/exp OR barium:ti,ab OR micropaque:ti,ab OR 'e z cat':ti,ab OR polibar:ti,ab OR barite:ti,ab OR baritop:ti,ab) AND ('nephrogenic systemic fibrosis'/exp/mj OR 'nephrogenic systemic fibros*':ti OR nsf:ti OR 'nephrogenic fibrosing dermopath*':ti OR nfd:ti)) AND ([dutch]/lim OR [english]/lim) NOT [conference abstract]/lim AND [2000-2018]/py Filter SR: ('meta analysis'/de OR cochrane:ab OR embase:ab OR psycinfo:ab OR cinahl:ab OR medline:ab OR ((systematic NEAR/1 (review OR overview)):ab,ti) OR ((meta NEAR/1 analy*):ab,ti) OR metaanalys*:ab,ti OR 'data extraction':ab OR cochrane:jt OR 'systematic review'/de) NOT (('animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp) = 11 Filter RCT: ('clinical trial'/exp OR 'randomization'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp OR 'placebo'/exp OR 'prospective study'/exp OR rct:ab,ti OR random*:ab,ti OR 'single blind':ab,ti OR 'randomised controlled trial':ab,ti OR 'randomized controlled trial'/exp OR placebo*:ab,ti) NOT 'conference abstract':it = 23 Filter observationele studies: 'clinical study'/de OR 'case control study'/de OR 'family study'/de OR 'longitudinal study'/de OR 'retrospective study'/de OR ('prospective study'/de NOT 'randomized controlled trial'/de) OR 'cohort analysis'/de OR ((cohort NEAR/1 (study OR studies)):ab,ti) OR (case:ab,ti AND ((control NEAR/1 (study OR studies)):ab,ti)) OR (follow:ab,ti AND ((up NEAR/1 (study OR studies)):ab,ti)) OR ((observational NEAR/1 (study OR studies)):ab,ti) OR ((epidemiologic NEAR/1 (study OR studies)):ab,ti) OR (('cross sectional' NEAR/1 (study OR studies)):ab,ti) = 59 = 82 uniek	

Exclusion Table

After full text review

Author (year)	Reasons for exclusion
Andrews (2008)	Not original research: comment
Broome (2007)	Does not meet PICO criteria: no intervention/measures
Coletti (2008)	Not original research: comment
Dawson (2008)	Not original research: narrative
Dawson (2008)	Not original research: comment
Gheuens (2014)	Does not meet PICO criteria: no intervention NSF
Kitajima (2012)	No original research: narrative
Knopp (2008)	Does not meet PICO criteria: no intervention/measures
Murashima (2008)	Does not meet PICO criteria: no intervention NSF
Nicolas (2012)	Does not meet PICO criteria: no intervention/measures comparative research
Panesar (2010)	Does not meet PICO criteria: no intervention
Perazella (2008)	Not original research: guideline
Perazella (2009)	Not original research: narrative
Prince (2008)	Does not meet PICO criteria: no intervention/measures
Prince (2009)	Does not meet PICO criteria: no intervention/measures
Rodby (2008)	Not original research: narrative
Saab (2007)	Not original research: comment
Sena (2010)	Does not meet PICO criteria: no intervention NSF
Silberzweig (2009)	Not original research: narrative
Swaminathan (2007)	Not original research: narrative
Thomsen (2007)	Not original research: guideline
Thomsen (2008)	Not original research: narrative
Thomsen (2013)	Not original research: guideline
Tran (2009)	Does not meet PICO criteria: no prevention
Wiginton (2008)	Does not meet PICO criteria: no intervention/measures
Yantasee (2010)	Not original research: narrative
Yee (2017)	Not original research: editorial
Zhang (2015)	Does not meet PICO criteria: no intervention/measures
Zou (2011)	No original research: narrative

Literature Search research question 7b

Database	Search String	Total
PubMed 1996 – March 2018	((Gadolinium-based[tiab] OR "Gadolinium"[Mesh] OR gadolinium[tiab] OR magnetic resonance contrast agent*[tiab] OR MR contrast agent*[tiab] OR magnetic resonance contrast media[tiab] OR MR contrast media[tiab] OR MRI contrast agent*[tiab] OR MRI contrast medium[tiab] OR MRI contrast media[tiab] OR GBCA*[tiab] OR Primovist[tiab] OR Eovist[tiab] OR Omniscan[tiab] OR Magnevist[tiab] OR Optimark[tiab] OR Prohance[tiab] OR Multihance[tiab] OR Dotarem[tiab] OR Gadovist[tiab] OR gadodiamide[tiab] OR gadopentetate[tiab] OR gadoversetamide[tiab] OR gadoteridol[tiab] OR gadobenate[tiab] OR gadoterate[tiab] OR gadobutrol[tiab] OR gadoxetic acid[tiab] OR gadoxetate disodium[tiab] OR "Gadolinium DTPA"[Mesh] OR Gd-DTPA[tiab] OR Gd-HP-DO3A[tiab] OR Gd-DTPA-BMA[tiab] OR Gd-DOTA[tiab] OR Gd-DTPA-BMEA[tiab] OR Gd-BOPTA[tiab] OR Gd-BT-DO3A[tiab] OR Gd-EOB-DTPA[tiab] OR meglumine[tiab] OR dimeglumine[tiab] OR ultrasound contrast agent*[tiab] OR US contrast agent*[tiab] OR ultrasound contrast medi*[tiab] OR Sonovue[tiab] OR Optison[tiab] OR perflutren[tiab] OR hexafluoride[tiab] OR "Barium"[Mesh] OR Barium[tiab] OR Micropaque[tiab] OR E-Z-CAT[tiab] OR E Z CAT[tiab] OR Polibar[tiab] OR Barite[tiab] OR Baritop[tiab]) AND ("Nephrogenic Fibrosing Dermopathy"[Mesh] OR Nephrogenic systemic fibros* [tiab] OR NSF [tiab] OR Nephrogenic fibrosing dermopath* [tiab] OR NFD[tiab]) AND (prevent*[tiab] OR "prevention and control" [Subheading]) AND (("1996/01/01"[PDat] : "3000/12/31"[PDat]) AND English[lang])) NOT (animals[mh] NOT humans[mh]) = 109	142
Embase (Elsevier)	(('gadolinium-based':ti,ab OR 'gadolinium'/exp OR gadolinium:ti,ab OR 'magnetic resonance contrast agent*':ti,ab OR 'mr contrast agent*':ti,ab OR 'magnetic resonance contrast media':ti,ab OR 'mr contrast media':ti,ab OR 'mri contrast agent*':ti,ab OR 'mri contrast medium':ti,ab OR 'mri contrast media':ti,ab OR gbca*:ti,ab OR primovist:ti,ab OR eovist:ti,ab OR omniscan:ti,ab OR magnevist:ti,ab OR optimark:ti,ab OR prohance:ti,ab OR multihance:ti,ab OR dotarem:ti,ab OR gadovist:ti,ab OR gadodiamide:ti,ab OR gadopentetate:ti,ab OR gadoversetamide:ti,ab OR gadoteridol:ti,ab OR gadobenate:ti,ab OR gadoterate:ti,ab OR gadobutrol:ti,ab OR 'gadoxetic acid':ti,ab OR 'gadoxetate disodium':ti,ab OR 'gd dtpa':ti,ab OR 'gd hp do3a':ti,ab OR 'gd dtpa bma':ti,ab OR 'gd dota':ti,ab OR 'gd dtpa bmea':ti,ab OR 'gd bopta':ti,ab OR 'gd bt do3a':ti,ab OR 'gd eob dtpa':ti,ab OR meglumine:ti,ab OR dimeglumine:ti,ab OR 'ultrasound contrast agent*':ti,ab OR 'us contrast agent*':ti,ab OR 'ultrasound contrast medi*':ti,ab OR sonovue:ti,ab OR optison:ti,ab OR perflutren:ti,ab OR hexafluoride:ti,ab OR 'barium'/exp OR barium:ti,ab OR micropaque:ti,ab OR 'e z cat':ti,ab OR polibar:ti,ab OR barite:ti,ab OR baritop:ti,ab) AND ('nephrogenic systemic fibrosis'/exp OR 'nephrogenic systemic fibros*':ti,ab OR nsf:ti,ab OR 'nephrogenic fibrosing dermopath*':ti,ab OR nfd:ti,ab) AND (prevent*:ti,ab OR 'prevention and control'/exp)) AND [english]/lim AND [1996-2018]/py NOT 'conference abstract':it NOT ([animals]/lim NOT [humans]/lim) = 84	

Appendices to module 8

Knowledge gaps

It is not clear what the clinical relevance is of gadolinium-based contrast agent (GBCA) induced T_1w hyperintensity of the nucleus dentatus and the globus pallidus in the brain?

Indicators

None.

Implementation

Recommendation	Time frame for implementation: <1 year, 1 to 3 years or >3 years	Expected effect on costs	Limitations for implementation	Barriers to implementation[1]	Actions needed for implementation[2]	Parties responsible for actions[3]	Other remarks
Ensure a strict indication for gadolinium-enhanced MRI and use EMA-approved GBCA in all patients to minimize possible gadolinium deposition.	**1 to 3 years**	**None**	**Lack of knowledge of guideline**	**Lack of knowledge of guideline**	**Dissemination of guideline**	**NVvR**	

[1] Barriers can be found at multiple levels. They can exist at the level of the consultant, the hospital organisation, and the health care system.

[2] Actions needed for implementation, but also actions to promote implementatie. Think about checks during quality visits, guideline publication, information of hospital management, et cetera.

[3] Who is responsible for implementation of recommendations will largely be determined by the level where the barriers are expected to be.

Exclusion table

Table of Excluded studies after reading full text

Author and year	Reason for exclusion
Abraham, 2008	Does not meet selection criteria.
Aruyani 2018	Does not meet selection criteria.
Adin, 2018	Does not meet selection criteria.
Arsenault, 1996	Does not meet selection criteria.
Bae, 2017	Does not meet selection criteria.
Behzadi, 2018	Does not meet selection criteria.
Bhargava, 2018	Does not meet selection criteria.
Bjornerund, 2017	Does not meet selection criteria.
Bolles, 2018	Does not meet selection criteria.
Boyken, 2018	Does not meet selection criteria.
Cao, 2016	Does not meet selection criteria.
Cao, 2016_1	Does not meet selection criteria.
Conte, 2017	Does not meet selection criteria.
Costa, 2018	Not an original article.
Costa, 2018_1	Does not meet selection criteria.
DiGregorio 2018	Does not meet selection criteria.
Errante, 2014	Does not meet selection criteria.
Fingerhut, 2018	Does not meet selection criteria.
Fingerhut, 2018_1	Does not meet selection criteria.
Flood 2017	Does not meet selection criteria.
Frenzel, 2017	Does not meet selection criteria
Frettelier, 2018	Does not meet selection criteria.

Guo, 2018	Does not meet selection criteria.
Hinoda, 2017	Does not meet selection criteria.
Hu, 2016	Does not meet selection criteria.
Huckle, 2016	Not an original article, narrative review.
Ichiwana, 2017	Does not meet selection criteria.
Idee, 2018	Does not meet selection criteria.
Idee, 2018_1	Does not meet selection criteria.
Jaulant, 2018	Does not meet selection criteria.
Jost, 2016	Does not meet selection criteria.
Kahn, 2017	Does not meet selection criteria.
Kanda, 2014	Does not meet selection criteria.
Kanda, 2015	Does not meet selection criteria.
Kang, 2018	Does not meet selection criteria.
Kang, 2018_1	Does not meet selection criteria.
Kasper, 2018	Does not meet selection criteria.
Khant, 2017	Does not meet selection criteria.
Kim, 2018	Does not meet selection criteria.
Kinner, 2018	Does not meet selection criteria.
Kralik, 2018	Does not meet selection criteria.
Kromrey, 2017	Does not meet selection criteria.
Kuno, 2017	Does not meet selection criteria.
Langer, 2017	Does not meet selection criteria.
Lee 2017	Does not meet selection criteria.
Lohrke, 2017	Does not meet selection criteria.
Lord, 2018	Does not meet selection criteria.
Malhotra, 2018	Does not meet selection criteria.
Maria, 2018	Does not meet selection criteria.
McDonald, 2018	Does not meet selection criteria.
McDonald, 2017	Does not meet selection criteria.
McDonald, 2017	Does not meet selection criteria.
Moser, 2018	Does not meet selection criteria.
Murata, 2016	Does not meet selection criteria.
Olchowy, 2017	Does not meet selection criteria, no comparative studies included in review.
Ozturk, 2018	Does not meet selection criteria.
Pasquini, 2018	Does not meet selection criteria.
Perrotta, 2017	Does not meet selection criteria.
Pinter, 2016	Does not meet selection criteria
Pulcino, 2018	Does not meet selection criteria.
Quattrocchi, 2018	Does not meet selection criteria.
Quattrocchi, 2015	Does not meet selection criteria.
Radbruch, 2018	Does not meet selection criteria.
Radbruch, 2017	Does not meet selection criteria.
Radbruch 2017_1	Does not meet selection criteria.
Radbruch, 2015	Does not meet selection criteria.
Radbruch, 2015	Does not meet selection criteria.
Ramalho, 2017	Does not meet selection criteria.
Ramalho, 2016	Does not meet selection criteria.
Ramalho, 2016_1	Does not meet selection criteria.
Ramalho 2016_2	Does not meet selection criteria.
Ramalho, 2015	Does not meet selection criteria.
Rasschaert, 2018	Does not meet selection criteria.
Raynaldo, 2018	Does not meet selection criteria.
Renz, 2018	Does not meet selection criteria.
Roberts, 2017	Does not meet selection criteria.
Roberts, 2017_1	Does not meet selection criteria.
Rossi, 2017	Does not meet selection criteria.
Runge 2017	Does not meet selection criteria.
Ryo, 2018	Does not meet selection criteria.
Schlemm, 2017	Does not meet selection criteria.
Schneider, 2016	Does not meet selection criteria

Splendiani, 2018	Does not meet selection criteria.
Swaminathan, 2016	Does not meet selection criteria.
Tamrazi, 2018	Does not meet selection criteria.
Tamrazi, 2018_1	Does not meet selection criteria.
Taoka, 2018	Does not meet selection criteria.
Taoka, 2018_1	Does not meet selection criteria..
Tedeschi, 2018	Does not meet selection criteria.
Tedeschi 2018_1	Does not meet selection criteria.
Thomsen, 2016	Does not meet selection criteria.
Tibussek, 2017	Does not meet selection criteria.
Weberling, 2015	Does not meet selection criteria.
Xia, 2014	Does not meet selection criteria.
Yoo, 2018	Does not meet selection criteria.
Young, 2017	Does not meet selection criteria.
Young, 2018	Does not meet selection criteria, patient population consists of children.
Young, 2018_1	Does not meet selection criteria.
Zhang, 2017	Does not meet selection criteria.

Search string

Database	ZSearch string	Total
PubMed 1996 – November 2018	((Gadolinium-based[ti] OR "Gadolinium"[Majr] OR gadolinium[ti] OR magnetic resonance contrast agent*[ti] OR MR contrast agent*[ti] OR magnetic resonance contrast media[ti] OR MR contrast media[ti] OR MRI contrast agent*[ti] OR MRI contrast medium[ti] OR MRI contrast media[ti] OR GBCA*[ti] OR Primovist[ti] OR Eovist[ti] OR Omniscan[ti] OR Magnevist[ti] OR Optimark[ti] OR Prohance[ti] OR Multihance[ti] OR Dotarem[ti] OR Gadovist[ti] OR gadodiamide[ti] OR gadopentetate[ti] OR gadoversetamide[ti] OR gadoteridol[ti] OR gadobenate[ti] OR gadoterate[ti] OR gadobutrol[ti] OR gadoxetic acid[ti] OR gadoxetate disodium[ti] OR "Gadolinium DTPA"[Majr] OR Gd-DTPA[ti] OR Gd-HP-DO3A[ti] OR Gd-DTPA-BMA[ti] OR Gd-DOTA[ti] OR Gd-DTPA-BMEA[ti] OR Gd-BOPTA[ti] OR Gd-BT-DO3A[ti] OR Gd-EOB-DTPA[ti] OR meglumine[ti] OR dimeglumine[ti] OR ultrasound contrast agent*[ti] OR US contrast agent*[ti] OR ultrasound contrast medi*[ti] OR Sonovue[ti] OR Optison[ti] OR perflutren[ti] OR hexafluoride[ti] OR "Barium"[Mesh] OR Barium[ti] OR Micropaque[ti] OR E-Z-CAT[ti] OR E Z CAT[ti] OR Polibar[ti] OR Barite[ti] OR Baritop[ti]) AND ("Basal Ganglia"[Majr] OR "Cerebellar Nuclei"[Majr] OR "Globus Pallidus"[Majr] OR "Brain"[Majr] OR "Tissues"[Majr] OR "Liver"[Majr] OR "Bone and Bones"[Majr] OR "Parkinson Disease"[Majr] OR basal gangli*[ti] OR dentate nucleus[ti] OR globus pallidus[ti] OR brain[ti] OR intracranial[ti] OR bone[ti] OR liver[ti] OR tissue*[ti] OR renal[ti] OR parkinson*[ti]) AND (accumulate*[tiab] OR deposition*[tiab] OR signal intensit*[tiab] OR signal increase*[tiab] OR hyperintensity[tiab] OR hypersignal*[tiab] OR toxicit*[tiab] OR exposure[tiab]) AND (("1996/01/01"[PDat] : "3000/12/31"[PDat]) AND English[lang])) NOT (animals[mh] NOT humans[mh]) = 560 Systematic Reviews: ((review[tiab] OR "Review"[Publication Type] OR "Meta-Analysis as Topic"[Mesh] OR meta-analysis[tiab] OR "Meta-Analysis "[Publication Type]) NOT ("Letter"[Publication Type] OR "Editorial"[Publication Type] OR "Comment"[Publication Type])) NOT ("Animals"[Mesh] NOT ("Animals"[Mesh] AND "Humans"[Mesh])) 96 Randomized Controlled Trials: randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR placebo[tiab] OR drug therapy[sh] OR randomly[tiab] OR trial[tiab] OR groups[tiab] 80 Observationele studies: "cohort studies"[mesh] OR "case-control studies"[mesh] OR "comparative	722 (360 SR's, RCT's en Observationele studies + 362 overige studies)

	study"[pt] OR "risk factors"[mesh] OR "cohort"[tw] OR "compared"[tw] OR "groups"[tw] OR "case control"[tw] OR "multivariate"[tw] 312 Overige studies: 152	
Embase (Elsevier)	('gadolinium-based':ti OR 'gadolinium'/exp/mj OR gadolinium*:ti OR 'magnetic resonance contrast agent*':ti OR 'mr contrast agent*':ti OR 'magnetic resonance contrast media':ti OR 'mr contrast media':ti OR 'mri contrast agent*':ti OR 'mri contrast medium':ti OR 'mri contrast media':ti OR gbca*:ti OR primovist:ti OR eovist:ti OR omniscan:ti OR magnevist:ti OR optimark:ti OR prohance:ti OR multihance:ti OR dotarem:ti OR gadovist:ti OR gadodiamide:ti OR gadopentetate:ti OR gadoversetamide:ti OR gadoteridol:ti OR gadobenate:ti OR gadoterate:ti OR gadobutrol:ti OR 'gadoxetic acid':ti OR 'gadoxetate disodium':ti OR 'gd dtpa':ti OR 'gd hp do3a':ti OR 'gd dtpa bma':ti OR 'gd dota':ti OR 'gd dtpa bmea':ti OR 'gd bopta':ti OR 'gd bt do3a':ti OR 'gd eob dtpa':ti OR meglumine:ti OR dimeglumine:ti OR 'ultrasound contrast agent*':ti OR 'us contrast agent*':ti OR 'ultrasound contrast medi*':ti OR sonovue:ti OR optison:ti OR perflutren:ti OR hexafluoride:ti OR 'barium'/exp/mj OR barium:ti OR micropaque:ti OR 'e z cat':ti OR polibar:ti OR barite:ti OR baritop:ti) AND ('basal ganglion'/exp/mj OR 'basal gangli*':ti OR 'dentate nucleus'/exp/mj OR 'dentate nucleus':ti OR 'globus pallidus'/exp/mj OR 'globus pallidus':ti OR 'brain'/exp/mj OR brain:ti OR intracranial:ti OR bone:ti OR liver:ti OR tissue*:ti OR renal:ti OR parkinson*:ti OR 'tissues'/exp/mj OR 'liver'/exp/mj OR 'bone'/exp/mj OR 'parkinson disease'/exp/mj) AND (accumulate*:ti,ab OR deposition*:ti,ab OR 'signal intensit*':ti,ab OR 'signal increase*':ti,ab OR hyperintensity:ti,ab OR hypersignal*:ti,ab OR toxicit*:ti,ab OR exposure:ti,ab) AND [english]/lim AND [1996-2018]/py NOT 'conference abstract':it = 535 Systematic Reviews: ('meta analysis'/de OR cochrane:ab OR embase:ab OR psycinfo:ab OR cinahl:ab OR medline:ab OR ((systematic NEAR/1 (review OR overview)):ab,ti) OR ((meta NEAR/1 analy*):ab,ti) OR metaanalys*:ab,ti OR 'data extraction':ab OR cochrane:jt OR 'systematic review'/de) NOT (('animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp) 4 Randomized Controlled Trials: ('clinical trial'/exp OR 'randomization'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp OR 'placebo'/exp OR 'prospective study'/exp OR rct:ab,ti OR random*:ab,ti OR 'single blind':ab,ti OR 'randomised controlled trial':ab,ti OR 'randomized controlled trial'/exp OR placebo*:ab,ti) NOT 'conference abstract':it 81 Observationele studies: 'clinical study'/de OR 'case control study'/de OR 'family study'/de OR 'longitudinal study'/de OR 'retrospective study'/de OR ('prospective study'/de NOT 'randomized controlled trial'/de) OR 'cohort analysis'/de OR ((cohort NEAR/1 (study OR studies)):ab,ti) OR (case:ab,ti AND ((control NEAR/1 (study OR studies)):ab,ti)) OR (follow:ab,ti AND ((up NEAR/1 (study OR studies)):ab,ti)) OR ((observational NEAR/1 (study OR studies)):ab,ti) OR ((epidemiologic NEAR/1 (study OR studies)):ab,ti) OR (('cross sectional' NEAR/1 (study OR studies)):ab,ti) 133 Overige studies: 317	

Appendices to module 9

Knowledge Gaps

It is not clear what the safety and efficacy is of contrast administration with haemodialysis catheters versus peripheral intravenous access sites.

It is not clear what the effect is on image quality when contrast power injection is performed using CVCs, HD catheters, PICCs and TIVAPs versus peripheral catheters.

Quality Indicators

None.

Implementation

Recommendation	Time frame for implementation: <1 year, 1 to 3years or >3 years	Expected effect on costs	Limitations for implementation	Barriers to implementation[1]	Actions needed for implementation[2]	Parties responsible for actions[3]	Other remarks
Use a peripheral venous access catheter for IV power injected contrast administration to obtain the best quality level of contrast images.	1 to 3 years	None	Lack of knowledge of guideline	Lack of knowledge of guideline	Dissemination of guideline	NVvR	
Check the position of the CVC TIVAD or PICC line and its patency before and after the power injected contrast administration, when a peripheral venous access catheter is unavailable.	1 to 3 years	None	Lack of knowledge of guideline	Lack of knowledge of guideline	Dissemination of guideline	NVvR	
When optimal quality of contrast-enhanced images in CT is needed, the use of a power injector and a peripheral venous access catheter for IV contrast administration is recommended.	1 to 3 years	None	Lack of knowledge of guideline	Lack of knowledge of guideline	Dissemination of guideline	NVvR	
Power-injectable	1-3 years	None	Lack of knowledge of	Lack of knowledge of	Dissemination of guideline	NVvR	

central venous catheters may be safely used for administration of CM using a power injector, when recommendations of the catheter manufacturer are followed.			guideline	guideline			
Power-injectable haemodialysis catheters may be safely used for administration of CM using a power injector, when recommendations of the catheter manufacturer are followed.	1 to 3 years	None	Lack of knowledge of guideline	Lack of knowledge of guideline	Dissemination of guideline	NVvR	
There is a risk of catheter tip migration of PICCs and TIVADs when CM is injected via a power injector in patients with a catheter tip position above the tracheobronchial angle. When a power-injectable PICC or TIVAD is used for CM administration, check the position of the catheter tip with a CT scout radiograph before and after power-injection of CM.	1 to 3 years	None	Lack of knowledge of guideline	Lack of knowledge of guideline	Dissemination of guideline	NVvR	
When a power-injectable CVC, HC, PICC or TIVAD is used for CM administration with a power	1-3 years	None	Lack of knowledge of guideline	Lack of knowledge of guideline	Dissemination of guideline	NVvR	

injector, check the patency of the catheter after the procedure by manual flush of 20ml normal saline.							

[1] Barriers can be found at multiple levels. They can exist at the level of the consultant, the hospital organisation, and the health care system.

[2] Actions needed for implementation, but also actions to promote implementation. Think about checks during quality visits, guideline publication, information of hospital management, et cetera.

[3] Who is responsible for implementation of recommendations will largely be determined by the level where the barriers are expected to be.

Evidence tables

Not applicable, none of the studies fulfilled the inclusion criteria of the PICO.

Exclusion Table

Table Exclusion after full text review

Author and Year	Reasons for exclusion
Uslusoy, 2008	Does not fulfil PICO-criteria.
Teichgräber, 2011	Does not fulfil PICO-criteria.
Klee, 2011	Does not fulfil PICO-criteria: Pediatric population
Coyle, 2004	Included in SR Buijs, 2017
Herts, 2001	Included in SR Buijs, 2017
Kaste, 1996	Does not fulfil PICO-criteria.
Verity, 2017	Small sample size
Morden, 2014	Included in Buijs, 2017
Hardie, 2014	Does not fulfil PICO-criteria
MAcHt, 2012	Included in Buijs, 2017
Goltz, 2012	Included in Buijs, 2017
Alexander, 2012	No full-tekst available
Goltz, 2011	Included in Buijs, 2017
Wienbeck, 210	Does not fulfil PICO-criteria

Search strategy

Database	Search terms	Total
PubMed 1996 – May 2018	((("Contrast Media"[Mesh] OR contrast [tiab] OR radiocontrast [tiab] OR radiopaque [tiab] OR "Barium"[Mesh] OR barium [tiab] OR gadolinium [tiab] OR microbubble* [tiab]) AND ("Central Venous Catheters"[Mesh] OR "Catheterization, Central Venous"[Mesh] OR "Catheterization, Peripheral"[Mesh] OR "Vascular Access Devices"[Mesh] OR venous catheter* [tiab] OR central catheter* [tiab] OR Central line* [tiab] OR PICC [tiab] OR PICCs [tiab] OR CVP [tiab] OR central venous line* [tiab] OR CVC [tiab] OR CVL [tiab] OR PAC [tiab] OR port [tiab] OR ports [tiab] OR port-a-cath [tiab] OR hickman* [tiab] OR vein catheter* [tiab] OR CVAD* [tiab] OR vascular access device* [tiab] OR broviac [tiab]) AND (pump*[tiab] OR power inject*[tiab])) AND ("1996/01/01"[PDat] : "3000/12/31"[PDat]) AND English[lang]) = 82	= 96
Embase (Elsevier)	('contrast medium'/exp OR contrast:ti,ab OR radiocontrast:ti,ab OR radiopaque*:ab,ti OR 'barium'/exp OR barium:ab,ti OR 'gadolinium'/exp OR gadolinium:ab,ti OR 'microbubble'/exp OR microbubble*:ab,ti) AND ('central venous catheter'/exp OR 'vascular access device'/exp OR 'venous catheter*':ti,ab OR 'central catheter*':ti,ab OR 'central line*':ti,ab OR picc*:ti,ab OR cvp:ti,ab OR 'central venous line*':ti,ab OR cvc:ti,ab OR cvl:ti,ab OR pac:ti,ab OR port:ti,ab OR ports:ti,ab OR 'port-a-cath':ti,ab OR hickman*:ti,ab OR 'vein catheter':ti,ab OR cvad*:ti,ab OR 'vascular access device*':ti,ab OR	

	broviac:ti,ab) AND (pump*:ti,ab OR 'power inject*':ti,ab) AND [english]/lim AND [1996-2018]/py NOT 'conference abstract':it = 80	

Appendices to module 10

Knowledge Gaps

It is not clear what the best treatment is for contrast extravasation, and if any treatment is effective at all.

Indicators

None.

Implementation

Recommendation	Time frame for implementation: <1 year, 1 to 3years or >3 years	Expected effect on costs	Limitations for implementation	Barriers to implementation[1]	Actions needed for implementation[2]	Parties responsible for actions[3]	Other remarks
Consider the following treatment options for contrast extravasation: • Try to aspirate the extravasated contrast medium through an inserted needle • Mark affected area • Use compresses, for relieving pain at the injection site • Use pain killers • Elevate the affected extremity above the level of the heart.	1 to 3 years	None	Lack of knowledge of guideline	Lack of knowledge of guideline	Dissemination of guideline	NVvR	
Record contrast extravasation and treatment in the patient record (volume, CM concentration, area, clinical findings).	1-3 years	None	Lack of knowledge of guideline	Lack of knowledge of guideline	Dissemination of guideline	NVvR	
Give the patient clear instructions when to seek additional medical care:	1-3 years	None	Lack of knowledge of guideline	Lack of knowledge of guideline	Dissemination of guideline	NVvR	

• Any worsening of symptoms • Skin ulceration • Development of any neurologic or circulatory symptoms, including paraesthesia's • Give the patient a patient information leaflet.							
For severe extravasation injury: • Consult a plastic surgeon • Notify the referring physician.	1-3 years	None	Lack of knowledge of guideline	Lack of knowledge of guideline	Dissemination of guideline	NVvR	

[1] Barriers can be found at multiple levels. They can exist at the level of the consultant, the hospital organisation, and the health care system.
[2] Actions needed for implementation, but also actions to promote implementation. Think about checks during quality visits, guideline publication, information of hospital management, et cetera.
[3] Who is responsible for implementation of recommendations will largely be determined by the level where the barriers are expected to be.

Exclusion table

Table Exclusion after reading the full text

Author and Year	Reasons for exclusion
Bellin 2002	Does not fulfil selection criteria. No control group. Descriptive.
Botany 2010	Does not fulfil selection criteria. No control group. Descriptive.
Cochran 2002	Does not fulfil selection criteria. No control group. Descriptive.
Cohan 1997	Does not fulfil selection criteria. No control group. Descriptive.
Conner 2017	Does not fulfil selection criteria. No control group. Descriptive.
Conner 2017	Does not fulfil selection criteria. No control group. Descriptive.
Davenport 2012	Does not fulfil selection criteria. No control group. Descriptive.
Ding 2018	Does not discuss treatment of extravasation
Ding 2018	Does not fulfil selection criteria. No control group. Descriptive.
Earhart 2011	Does not fulfil selection criteria. No control group. Descriptive.
Fallscheer 2007	Does not fulfil selection criteria. No control group. Descriptive.
Kim 2017	Does not fulfil selection criteria. No control group. Descriptive.
Kim 2017	Does not fulfil selection criteria. No control group. Descriptive.
Nicola 2016	Does not fulfil selection criteria. No control group. Descriptive.
Rose 2015	Does not fulfil selection criteria. No control group. Descriptive.
Schaverien 2008	Does not fulfil selection criteria. No control group. Descriptive.
Schummer 2010	Does not fulfil selection criteria. No control group. Descriptive.
Sonis 2017	Does not fulfil selection criteria. No control group. Descriptive.
Sonis 2017	Does not fulfil selection criteria. No control group. Descriptive.
Sum 2006	Does not fulfil selection criteria. No control group. Descriptive.
Tonolini 2012	Does not fulfil selection criteria. No control group. Descriptive.

Tonolini 2016	No comparison therapies. Letter tot the editor on the occasion of Nicola 2016
Tsai 2007	Does not fulfil selection criteria. No control group. Descriptive.
Vandeweyer 2000	Does not fulfil selection criteria. No control group. Descriptive.
Wang 2007	Does not fulfil selection criteria. No control group. Descriptive.
Wilson 2011	Does not fulfil selection criteria. No control group. Descriptive.

Search Criteria

Database	Seatrch strings	Total
PubMed 1996 – February 2018	(("Extravasation of Diagnostic and Therapeutic Materials"[Mesh] OR extravasation* [tiab] OR compartment syndrome*[tiab]) AND ("Contrast Media"[Majr] OR contrast medi*[ti])) AND (("1996/01/01"[PDat] : "3000/12/31"[PDat]) AND (English[lang] OR Dutch[lang])) *Systematic Review filter:* (systematic*[tiab] AND (bibliographic*[TIAB] OR literature[tiab] OR review[tiab] OR reviewed[tiab] OR reviews[tiab])) OR (comprehensive*[TIAB] AND (bibliographic*[TIAB] OR literature[tiab])) OR "cochrane database syst rev"[Journal] OR "Evidence report/technology assessment (Summary)"[journal] OR "Evidence report/technology assessment"[journal] OR "integrative literature review"[tiab] OR "integrative research review"[tiab] OR "integrative review"[tiab] OR "research synthesis"[tiab] OR "research integration"[tiab] OR cinahl[tiab] OR embase[tiab] OR medline[tiab] OR psyclit[tiab] OR (psycinfo[tiab] NOT "psycinfo database"[tiab]) OR pubmed[tiab] OR scopus[tiab] OR "web of science"[tiab] OR "data synthesis"[tiab] OR meta-analys*[tiab] OR meta-analyz*[tiab] OR meta-analyt*[tiab] OR metaanalys*[tiab] OR metaanalyz*[tiab] OR metaanalyt*[tiab] OR "meta-analysis as topic"[MeSH:noexp] OR Meta-Analysis[ptyp] OR ((review[tiab] AND (rationale[tiab] OR evidence[tiab])) AND review[pt]) *RCT filter:* ((random*[tiab] AND (controlled[tiab] OR control[tiab] OR placebo[tiab] OR versus[tiab] OR versus[tiab] OR group[tiab] OR groups[tiab] OR comparison[tiab] OR compared[tiab] OR arm[tiab] OR arms[tiab] OR crossover[tiab] OR cross-over[tiab]) AND (trial[tiab] OR study[tiab])) OR ((single[tiab] OR double[tiab] OR triple[tiab]) AND (masked[tiab] OR blind*[tiab]))) OR ((random*[ot] AND (controlled[ot] OR control[ot] OR placebo[ot] OR versus[ot] OR versus[ot] OR group[ot] OR groups[ot] OR comparison[ot] OR compared[ot] OR arm[ot] OR arms[ot] OR crossover[ot] OR cross-over[ot]) AND (trial[ot] OR study[ot])) OR ((single[ot] OR double[ot] OR triple[ot]) AND (masked[ot] OR blind*[ot]))) = 319	480
Embase (Elsevier)	(('extravasation'/exp OR extravasation*:ab,ti OR 'compartment syndrom*':ab,ti) AND ('contrast medium'/exp/mj OR 'contrast medi*':ti) AND ([dutch]/lim OR [english]/lim) AND [1996-2018]/py) NOT 'conference abstract':it)) *Systematic Review filter*: (('meta analysis'/de OR cochrane:ab OR embase:ab OR psycinfo:ab OR cinahl:ab OR medline:ab OR ((systematic NEAR/1 (review OR overview)):ab,ti) OR ((meta NEAR/1 analy*):ab,ti) OR metaanalys*:ab,ti OR 'data extraction':ab OR cochrane:jt OR 'systematic review'/de) NOT (('animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp))) *RCT filter*: (('clinical trial'/exp OR 'randomization'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp OR 'placebo'/exp OR 'prospective study'/exp OR rct:ab,ti OR random*:ab,ti OR 'single blind':ab,ti OR 'randomised controlled trial':ab,ti OR 'randomized controlled trial'/exp OR placebo*:ab,ti) NOT 'conference abstract':it)) = 319	

Summary of knowledge gaps

Module 1
It is unclear which treatments of acute hypersensitivity reactions after CM administration lead to a higher severity of complaints. The following outcomes would be relevant to study: duration of acute reaction, morbidity, mortality, costs, hospitalization in an IC-unit, and length of stay.

Module 2
It is unclear whether any treatment of late hyper sensitivity reactons after contrast administration leads to a quicker recovery, a less serious course, sequelae, mortality, morbidity hospitalization. It is also not clear whether one treatment option might lead to a better outcome (as described in the previous sentence) compared to another.

Module 3
It is not clear whether serum tests for hypersensitivity reactions after contrast administration lead to a better probability of a correct diagnosis, and ultimately, a better patient outcome (measured as less recurrent hypersensitivity reactions after contrast administration, less morbidity and mortality).

Module 4
It is unclear whether application of cutaneous tests (skin test, patch test (PT), Intradermal test (IDT), skin prick test (SPT) or scratch test) in patients who have had an acute hypersensitivity reaction after contrast medium administration leads to a better correctly confirmed diagnosis of hypersensitivity reaction.

It is unclear which contrast media should be included in a panel for cutaneous tests.

Module 5
What factors are related to an increased risk of developing hypersensitivity reactions after contrast administration?

What are the effects of a prophylactic measure to prevent hypersensitivity reactions after contrast administration compared to a different/ control measure to prevent hypersensitivity reactions after contrast administration or to no prophylactic measure, in patients undergoing radiological examinations with contrast media?

Module 6
The incidence of PC-AKI after administration of GBCA is unknown.

The difference in nephrotoxic potential between different GBCA's is unknown.

Module 7
It is unclear whether ionic macrocyclic GBCAs compared to non-ionic macrocyclic GBCAs in renal insufficiency patients (eGFR <30 ml/min/1.73m^2) are associated with different risk of NSF.

It is unclear whether residual kidney function in dialysis patients is affected by the timing of haemodialysis after administration of GBCA.

It is unclear whether timing of dialysis after administration of GBCA affects patient outcomes.

Module 8
It is not clear what the clinical relevance is of gadolinium-based contrast agent (GBCA) induced T_1w hyperintensity of the nucleus dentatus and the globus pallidus in the brain?

Module 9

It is not clear what the safety and efficacy is of contrast administration with haemodialysis catheters versus peripheral intravenous access sites.

It is not clear what the effect is on image quality when contrast power injection is performed using CVCs, HD catheters, PICCs and TIVAPs versus peripheral catheters.

Module 10

It is not clear what the best treatment is for contrast extravasation, and if any treatment is effective at all.