Assessment of ‘established medical science and medical practice’: a technical modification

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Summary

The Netherlands introduced the *Zorgverzekeringswet* (Health Insurance Act) to provide health insurance with a broad package of care for all its citizens. An important key aspect is that care is only included in the insured standard health care benefit package if it is regarded as effective. The phrase used to describe this in the legislation is: the care must comply with 'established medical science and medical practice'.

Zorginstituut Nederland (hereafter: the *Zorginstituut*) has established an assessment framework for its method for deciding whether care complies with the above-mentioned statutory criterion. The *Zorginstituut* uses this framework (recorded in the report "Established Science and Medical Practice" dated January 2015) for assessments carried out by the *Zorginstituut* in its capacity as manager of the standard package.

During recent years these assessments frequently involved the question of whether the assessment might be of a technical modification of an intervention already included in the insured package. This was followed by the question: if it is a technical modification, does this warrant concluding that the technical modification is also included in the insured package or is a separate assessment (of 'established medical science and medical practice') needed?

In this report, the *Zorginstituut* presents a framework that can be used for answering this type of question as and when needed. The purpose is to ensure that our work is as systematic, consistent and transparent as possible when making assessments that may involve a technical modification of an intervention whose effectiveness has been established or is not open to discussion. This is a supplement to the general assessment framework 'established medical science and medical practice' dating from 2015.

Introduction

Over the past few years, *Zorginstituut Nederland* (hereafter: the *Zorginstituut*) has frequently issued assessments whereby questions were raised about whether one could speak of a technical modification of an intervention that is already included in the insured package. This was followed by the question: if it is a technical modification, does this warrant the (immediate) conclusion that the technical modification is thus included in the insured package or is a separate assessment (of 'established medical science and medical practice') needed?

Below we discuss the concept of technical modification, our aim being to record and elaborate on our method of assessment in order to promote consistency and transparency. As input we made use of an analysis of assessments over the past few years in which the concept of technical modification played a role. This involved looking at which arguments were used to prove that a case did involve a technical modification and – if it did – which approach we subsequently followed in forming a conclusion on 'established medical science and medical practice'. We also searched the literature for points of departure in order to define the concept of technical modification and how it should be assessed.

The next section first discusses briefly the concept of technical modification. This is followed by a framework that can be used to assess topics and files that may involve a technical modification of an intervention whose effectiveness has been established or is not open to discussion.

1 The concept of technical modification

1.1 General aspects

Over the course of time many interventional procedures are altered or undergo further development, by changing one or more aspects, e.g. to speed up patient recovery, shorten the duration of hospitalisation or increase ease of use for patients. This could involve a surgical intervention whereby the proposed resection is carried out endoscopically instead of as open surgery, or whereby the proposed operation route changes, e.g. from transforminal to transflaval. Manufacturers may introduce new products onto the market, such as implants or other medical devices, which are similar to an existing product and are (or can be) used by doctors for the same purpose. These too could involve minor variations in different products. Another possibility is that existing – effective – care is offered in the form of e-health and can be regarded as a modification of the original care.[1]

The collective term we can use for these situations is: technical modification.[2]

The conclusion that one can speak of a technical modification of an intervention whose effectiveness has been established or is not open to discussion does not mean that one can always (automatically) assume that the effectiveness of the technical modification has actually been established. That depends. Such a conclusion may be justified for some changes, e.g. a small change in the size of an incision to improve access during an operation (an example cited by NICE[3]). But what constitutes a small change, what constitutes a major change and when should one (actually) speak of a 'really' new intervention? Defining this precisely is difficult. NICE has this to say: "What precisely is a new intervention? If an existing intervention is modified, how much modification makes it new? If new technology is used for an established intervention, is that new?[4]

1.2 Assessing individual cases

The analysis of our past assessments reveals a lot of case-to-case diversity. Based on this, in our opinion it is difficult to define the concept of technical modification unambiguously and precisely. Nor can one define in advance when the effectiveness of a technical modification (assuming that this is what it is) can be deemed equal to that of the intervention on which the technical modification is based. Nor can clear points of departure for this be found in the literature either.

In each case it is necessary to determine (1) whether this is a technical modification, and if so, (2) what this means in relation to effectiveness. Can effectiveness data be extrapolated or will further assessment be needed? In other words: Can we (or can't we) assume that the technical modification, in view of the specific similarities and differences, is at least as effective as the existing intervention (is substantially equivalent to the existing intervention)?

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[1] Here too the question is whether the e-health application/modification can be equated with the care in its original form. The general line is that this is possible case if the contents and effectiveness of the e-health application do essentially differ from the original care.

[2] In the past we specifically used the term 'me-too products' or 'me-too medical devices' for a technical modification of a medical device. The term 'me-too' is also used in relation to medicinal care. A 'me-too medicinal product' is a product that is chemically practically identical to the first product in a given group. See footnote 49 of the report "Assessment of Established medical science and medical practice" dated 5 November 2007.

[3] Campbell B, Madden G. Safety and efficacy of interventional procedures. BMJ 2003; 326: 347-8.

[4] Campbell B, Morris R, Mandav L, et al. Identifying and selecting new procedures for health technology assessment: a decade of Nice experience. Int. J. Technol Assess Health Care 2014;30:454-60.

The following is a framework that can be used to answer these questions in individual cases. It is important to comment that this approach still involves an assessment of the statutory criterion 'established medical science and medical practice'. Our assessments are intended to promote a systematic examination of whether it is possible to declare – with scientific evidence – that the research results on the effectiveness of an existing intervention do or do not apply to a modification thereof.[5]

For the sake of clarity: in using the term effectiveness, we are referring to the broad concept of effectiveness that also covers the safety aspect.[6]

[5] In principle, the assessment, which follows certain steps, is based on scientific substantiation and can therefore be regarded as evidence-based.

[6] A detailed explanation of the concept of effectiveness can be found in the assessment framework relating to 'established medical science and medical practice'. Zee: CVZ. Assessment of established medical science and medical practice. Diemen, 2015.

2 Framework for assessing a technical modification

2.1 The main outline of the framework

It is important that our work is as systematic, consistent and transparent as possible in relation to assessments or questions that may involve a technical modification of an intervention that has already been assessed or an intervention whose effectiveness has been established or is not open to discussion. This is the purpose of the framework described below. It involves a number of steps and provides step-by-step information about relevant aspects and questions.

Step 1 > Does it involve a technical modification?

- If not, assess the individual merits of the intervention based on the system for assessing 'established medical science and medical practice'.[7] The assessment will include arguments for concluding that this intervention does not involve a technical modification.
- If the answer is yes, proceed to step 2.

Step 2 > It is a technical modification, but is the effectiveness of the technical modification equal to that of the original intervention?
In order to assess this, one needs to examine whether the effectiveness of the intervention could be affected by the modifications in the intervention. Then one has to weigh up whether the effectiveness of the technical modification is the same as that of the intervention that is being modified by the technical modification.

- If so, then further assessment of the technical modification against 'established medical science and medical practice' is not necessary/applicable. In that case, the question put to us regarding this matter can be dealt with briefly – but nevertheless providing evidence to substantiate the conclusion.[8]
- If the answer is no, then further assessment of the technical modification against 'established medical science and medical practice' is needed. Proceed to step 3.

Step 3 > It is a technical modification, but its effectiveness cannot simply be equated with that of the original intervention.
In that case, it will have to be assessed against 'established medical science and medical practice' in the usual way, thereby (where possible) taking into account (certain aspects of) the technical modification.[7]

The steps are explained in the next few paragraphs.

[7] The assessment framework regarding 'established medical science and medical practice' can be found in the following reports:
- CVZ. Assessment of Established Medical Science and Medical Practice. Diemen, 2015.
- CVZ. Medical tests. Assessment of Established Medical Science and Medical Practice. Diemen, 2011.
Both reports can be accessed via: www.zorginstituutnederland.nl

[8] The question may have arisen in response to a request put to the *Zorginstituut* by the SKGZ within the framework of a dispute between an insured person and their health insurer.

2.2 Explanation of step 1 (technical modification or not?)

The first question is whether it is a case of a technical modification. Determine this based on the following aspects/characteristics:

a. Determine – insofar as relevant – the similarities and differences between the intervention and the (possible) technical modification.
b. Discuss, based on the identified similarities and differences, why the intervention being assessed can/cannot be regarded as a technical modification.

Listing the similarities and differences provides information based on which one can weigh up whether or not this is – or appears to be – a technical modification. The following check-list can supply the right information.

Possible technical modification versus existing intervention	**Similarity**	**Difference**	**Explanation**
Type of treatment[9]			
Field of indication			
Treatment goal[10]			
Method of application/approach[11]			
Therapeutic area[12]			
Material usage[13]			
Mechanism of action[14]			
Biological parameters[15]			
Complexity[16]			
Other aspects			

2.3 Explanation of step 2 (can effectiveness data be extrapolated or not?)

The outcome of step 1 may be that it is a case of a technical modification. If so, then the next question is: can substantial equivalence be concluded (regarding an intervention that is deemed effective), meaning that the effectiveness of the technical modification has already been established?

To answer this question, estimate the consequences of the differences found against the similarities found for the degree of effectiveness of the technical modification.

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[9] For instance: the intervention and the modification both involve surgery or radiotherapy. It could be a modification or alternative to, e.g., a surgical intervention, i.e. now in the form of – for instance – chemotherapy. The essence/nature of this treatment differs from surgery. In general, this is not regarded as a technical modification.

[10] For instance: the original intervention and the modification have the same treatment goal, i.e. in both cases, radical removal of the tumour or decompression of a nerve end by removing the protrusion in the intervertebral disc.

[11] For instance: a different operative technique, e.g. open surgery versus endoscopic or minimal invasive surgery.

[12] For instance: a certain medical device or implant is effective and is used in a certain location, e.g. the pelvic floor. The therapeutic area is subsequently broadened by the proposed technical modification, e.g. to encompass the peritoneal cavity.

[13] For instance: fixating vertebrae with artificial bone instead of autologous or donor bone, or another filler for screw anchoring.

[14] For instance: the interventions have the same goal and mechanism of action, i.e. to destroy tumour tissue by local heat application. The heat is however generated by different means. Another example is: both interventions have the same mechanism of action, i.e. continuous glucose monitoring in cases of type 1 diabetes by means of interstitial measurement of glucose levels. In both interventions this is done with the help of a skin sensor, but with the technical modification the patient has to proactively scan the glucose levels him/herself.
Evidence of the mechanism of action should preferably be obtained by means of a literature search of solid scientific research.

[15] For instance: use of the same biologically active materials in contact with the same tissues.

[16] For instance: the modification is technically more complex and/or requires different (more) technical skills on the part of the care provider than the original intervention. Another example: the modification has/claims a different (greater) ease of use and/or requires different (more) skills on the part of the patient than the original intervention.

Essentially, this is an estimation of what the GRADE method refers to as 'indirectness'.[17] Discuss the implications of this. There are two possible outcomes:

a. Extrapolation is possible and no further assessment of 'established medical science and medical practice' is needed.
   In that case, one can argue that the effectiveness of the technical modification – in view of the similarities and differences found – is the same/equivalent to that of the intervention that has been technically modified. A quick scan of the literature providing evidence for the outcomes of the technical modification can (if available) act as a supporting argument. Another supporting argument could be supplied by a (preferably) evidence-based discussion of the opinions of the relevant professional group(s).
b. Extrapolation is not possible. Further assessment of 'established medical science and medical practice' is needed.
   In that case, in view of the similarities and differences found, there are indications or reasons for assuming or supposing that the outcomes and safety – the effectiveness of the technical modification – (significantly) differ from the effectiveness of the intervention that has been technically modified.[18]
   Indications/reasons can (also) be found by means of a quick scan of the literature on (evidence in favour of) the effectiveness of the technical modification (if available). The same applies to the (evidence-based) discussion of the opinion of the relevant professional group(s) and to the fact that the professional group(s) is/are still involved in carrying out specific effectiveness research into the intervention concerned or is/are appealing for reticence in using the 'new' techniques.

2.4 Explanation of step 3 ('full-dress' assessment of a technical modification)

It is a technical modification, but it requires further assessment of 'established medical science and medical practice' because the effectiveness of the intervention and the technical modification thereof cannot simply be equated with one another (outcome of steps 1 and 2).

In this case, the assessment of 'established medical science and medical practice' takes place in the usual way.[7] This must take into account (certain aspects of) the technical modification, e.g. in determining the appropriate research profile. If the intervention being assessed can – with evidence – be regarded as a technical modification of a current intervention (already regarded as effective), high-quality evidence of the effectiveness of the technical modification will not always be needed. This will differ from case to case. The ultimate conclusion will be based on the 'total body of evidence'.

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[17] GRADE stands for 'Grading of Recommendations Assessment, Development and Evaluation'. Using this method, it is possible to estimate the quality of all evidence of effectiveness that has been collected. One aspect that plays a role here is indirect evidence. See also section 3.2.4 of the assessment framework relating to 'established medical science and medical practice': Assessment of Established Medical Science and Medical Practice. CVZ, Diemen, 2015.

[18] This is in line with the approach of NICE. In section 5 of its IP (interventional procedures) programme manual, which reflects how NICE does effectiveness and safety assessments of interventions within the framework of treatment or a diagnosis, NICE says:
It is appropriate to notify NICE about an interventional procedure if:
- it is novel, with an unknown or uncertain efficacy and/or safety profile, or
- it is a variation of an established procedure that may have a different efficacy and/or safety profile from that of the established procedure
>>> Sometimes practitioners make minor alterations to established procedures and these do not merit notification, for example, a small change in the length or site of an incision to improve access in an operation.
>>> Interventional procedures involving robotics are generally considered a minor modification of their non robotic equivalent, and are therefore outside of the remit unless the procedure differs substantially because of the robotic element.
Consulting NICE in February 2019 via https://www.nice.org.uk/process/pmg28/chapter/notifications-to-the-programme.

2.5 Examples

Two examples from past assessments should serve to illustrate. The first example is a case in which we concluded – in view of the similarities and differences – that it was a technical modification and that one could assume that the effectiveness of the technical modification was comparable with the effectiveness of the intervention that had been technically modified.

Open microdiscectomy (MD) versus microendoscopic discectomy (MED)

Lumbar disc herniation (HNP) of the lumbar spine is a protrusion of an intervertebral disc. Pressure of the hernia on the nerve root can result in pain that radiates down the leg. Surgery becomes an option when conservative treatment has failed. Over the course of time, alongside open surgery (open microdiscectomy), the less invasive endoscopic technique (microendoscopic discectomy) has gained acceptance. Can the effectiveness of this technique be equated with that of open surgery? To answer this question, our approach was as follows.

Both treatments are used to treat lumbar herniation, the goal being to reduce compression of the root nerve by transflaval removal of the extrusion of the intervertebral disc. Thus, the same indication is involved, with the same treatment goal and the same access to the area on which surgery will take place. The difference between the two forms of treatment is the open approach (MD) versus the endoscopic approach (MED). In view of this, MED can be seen as a technical modification of MD. Furthermore, the effectiveness of both treatment options can be regarded as equivalent. The arguments in favour of this are:

- MED permits the possibility of progressing to the open method if necessary;
- Using MED, the surgical location can be visualised, if so desired, with a microscope, thus providing good visibility of the site to be operated on – just as with open surgery –, making it possible to avoid leaks in the dura mater and only removing part of the hernia.
- A quick-scan of the limited literature revealed no signs of any difference in effectiveness between the MED and the MD technique.

The second example is a case in which we concluded, despite it being a technical modification, that a separate assessment of the effectiveness of the technical modification was needed.

Radioembolisation with yttrium–90 microspheres versus with holmium-166

Radioembolisation with yttrium–90 microspheres is an effective treatment option for certain patients with inoperable liver tumours.[19] Does this also apply to treatment with holmium–166 microspheres that came onto the market at a later date? To answer this question, our approach was as follows.

The two forms of radioembolisation have a number of similarities:

- In both cases, tumour radiation takes place locally;
- Both types of microspheres are administered via a catheter into the hepatic artery;
- The same type of radiation is used (β–radiation) and the average energy of the β–radiation of van holmium–166 and yttrium–90 is approximately the same;
- The proposed radiation dose of the whole liver is approximately the same for both microspheres: 60 Gy on the whole liver with holmium–166 microspheres compared

[19] In 2011 and 2016 the *Zorginstituut* issued a positive assessment of radioembolisation with yttrium–90 microspheres for the indications inoperable HCC and non-resectable colorectal liver metastases, both in a salvage setting.

with 30–120 Gy with yttrium–90 microspheres.

In view of the many similarities between the microspheres, holmium–166 microspheres can be regarded as a technical modification of yttrium–90 microspheres. The biggest difference lies in the fact that different radioactive isotopes are used. Holmium–166 has a shorter half-life than yttrium–90, whereby the most important consequence is that the initial radiation dose is higher and the total amount of radiation is emitted in a shorter period of time. For this reason the biological effects of this more rapid emission of energy are not entirely clear. Moreover, uncertainty exists as to whether the effects of a more rapid emission of energy are the same for the various indications. This means that there may be a difference in effectiveness between holmium–166 and yttrium–90 and that a separate (more detailed) assessment of holmium–166 is needed.

The outcome of this assessment was that the indirect comparison of the results of studies into holmium–166 and yttrium–90 radioembolisation[20] indicates a similar effect of holmium–166 and yttrium–90 microspheres for the treatment of inoperable liver tumours. This outcome, added to the conclusion that holmium–166 can be regarded as a technical modification of yttrium–90 radioembolisation, leads to the conclusion that holmium–166 radioembolisation for the indication concerned can be regarded as effective treatment and therefore that it complies with 'established medical science and medical practice'.

[20] The assessment also took into account that, in this case – based on considerations arising from the so-called appropriate research-questionnaire –, the highest level of evidence was not necessary because holmium–166 microspheres can be regarded as a technical modification of yttrium–90 microspheres.

3 Supplement to the assessment framework

The above forms a supplement to the usual assessment framework that the *Zorginstituut* uses for assessing whether interventions comply with 'established medical science and medical practice'.[5] As mentioned earlier, the idea is to be as systematic, consistent and transparent as possible when making assessments and dealing with questions about a possible technical modification of an intervention that was assessed in the past or an intervention whose effectiveness has been established/is not open to discussion. In the long term, based on experience in using the described approach in practice, we will – if necessary – make changes and/or additions.

The *Zorginstituut* approved this supplement to the assessment framework 'established medical science and medical practice' on 23 April 2019. This supplement made use of the comments on the draft version of the *Zorginstituut*'s Care & Cure Committee (CCA-CCU) of the Scientific Advisory Board (WAR).

We sent this supplementary assessment framework to the Minister for Medical Care and Sport for information purposes.

Zorginstituut Nederland

Chair of the Executive Board

Sjaak Wijma