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Optimising the treatment of patients with long bone metastases

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Appendices

A. OPTIModel App

B. Study protocol for The OPTIMAL Study - a cmRCT

C. Validation and cross - cultural adaptation of the Toronto Extremity Salvage Score to Dutch

Appendix A.
OPTIModel App
A digital and online application

The OPTIModel application is designed to aid clinicians in the decision-making of any patient presenting with long bone metastases. The content of the application is based on the prognostic model as described in ***chapter 2*** and treatment recommendations as described in ***chapter 9***.

First, users are guided through a flowchart to estimate the remaining survival as shown in the screenshots in figure A.1.

Subsequently, users are guided through a second flowchart to receive a recommendation for local treatment, based on the initial survival estimation and the location, extent, and presentation of the metastasis as shown in the screenshots in figure A.2.

This application does not serve as treatment protocol and no rights may be derived from this information by physicians or patients.

The application can also be used on the following website: www.optimal-study.nl/tool (figure A.3).

The application can be downloaded (free of charge) in the Apple App Store and Google Play Store.

Apple App Store:

Google Play Store:

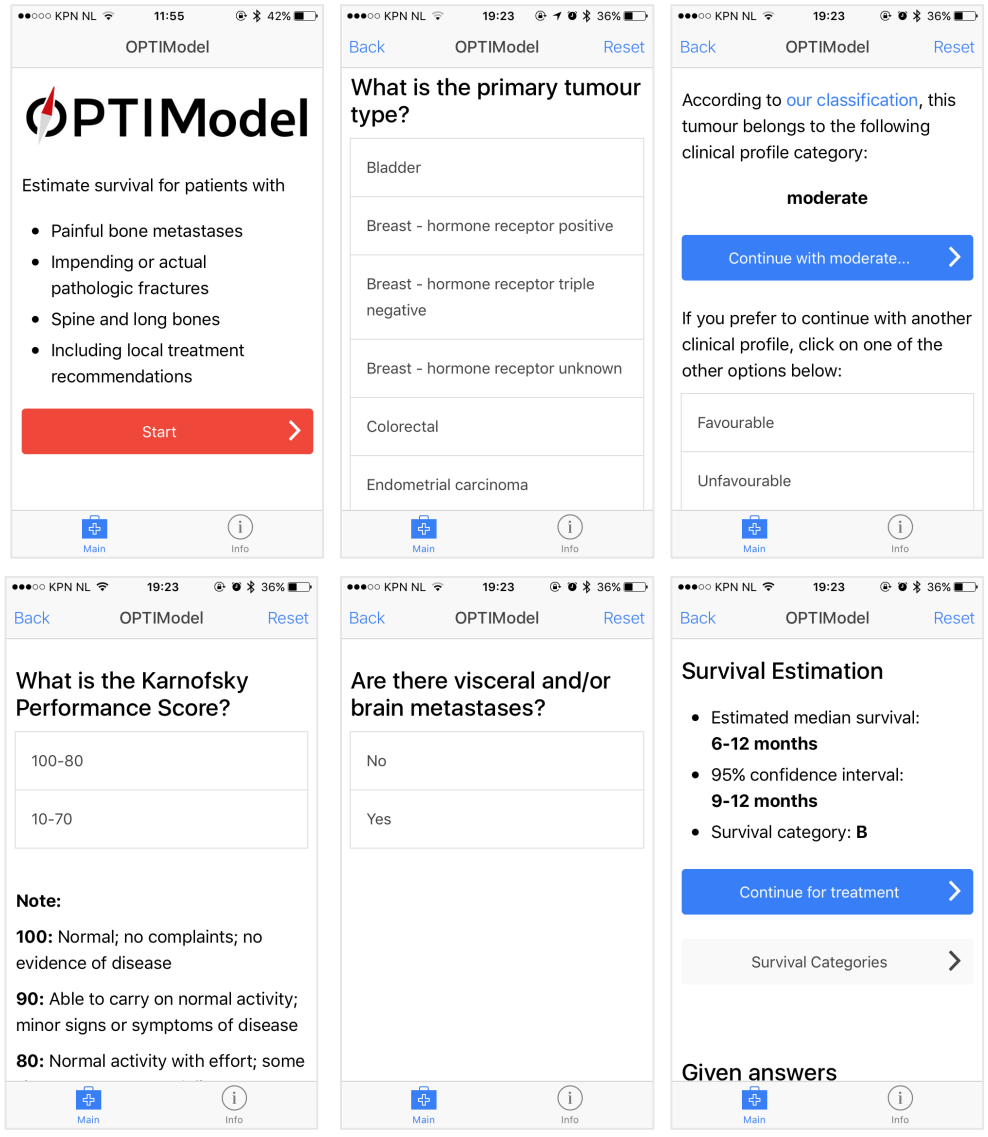

Figure A.1 Screenshots of the steps of the first part of the OPTIModel to estimate the remaining survival. As shown in the example in the last screenshot, the outcome is presented as estimated median survival (with 95% confidence interval) and the corresponding survival category according to the Optimal prognostic model (OPTIModel) as reported in chapter 2.

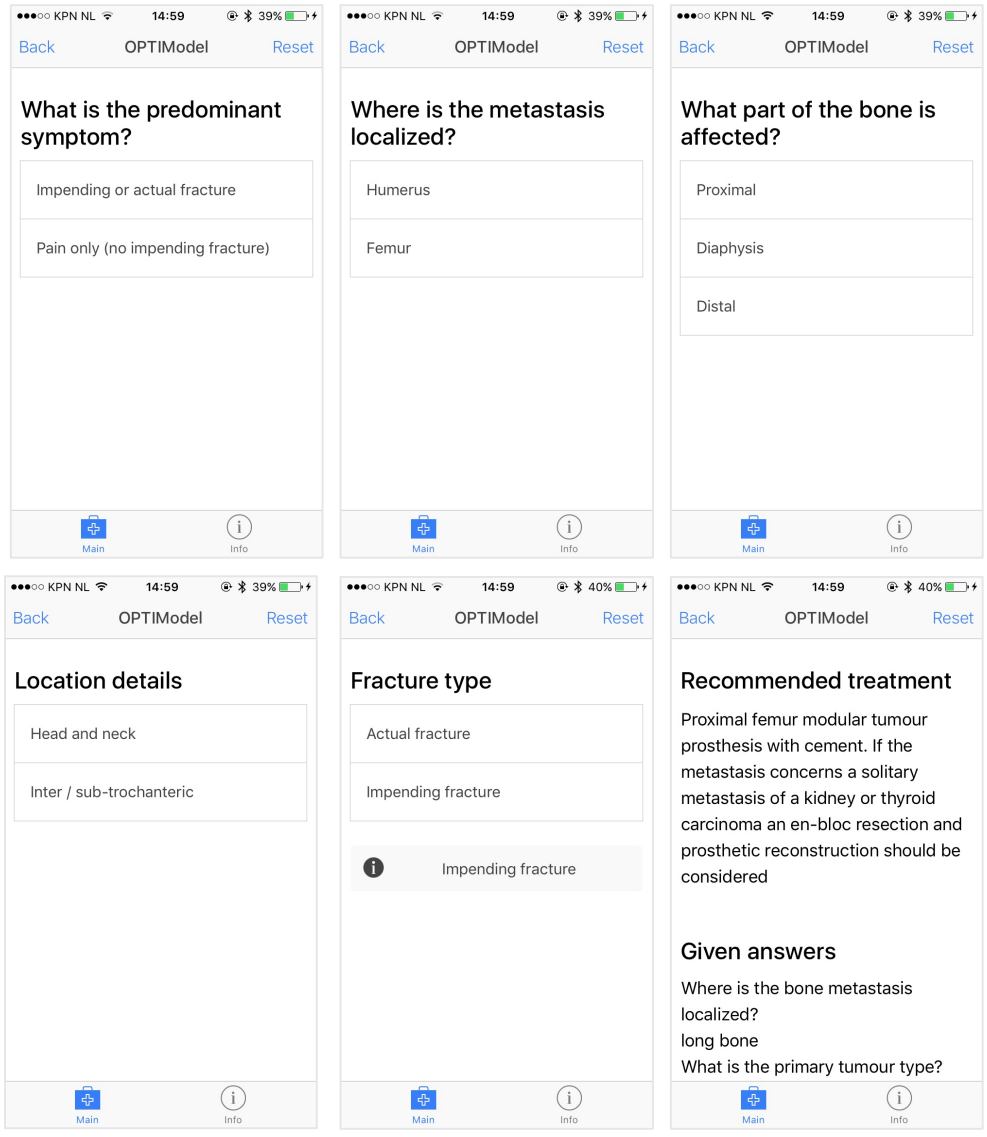

Figure A.2 Screenshots of the some of the steps of the second part of the OPTIModel that result in an advice for treatment (both radiotherapy or surgery) for symptomatic bone metastases of the humerus and femur.

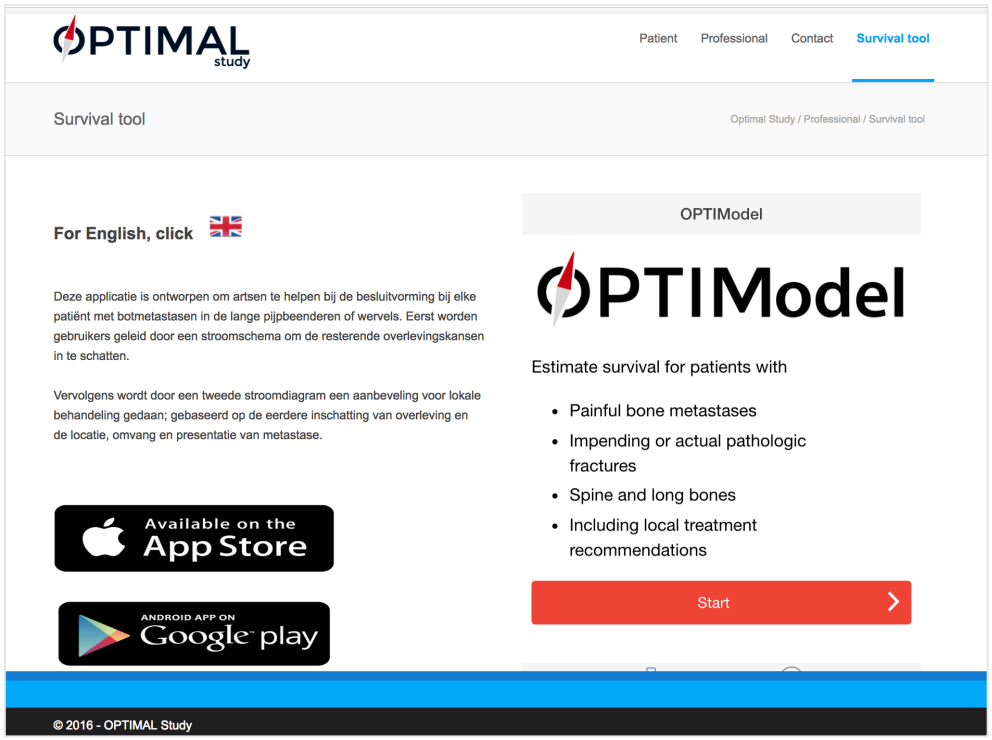

Figure A.3 Screenshot of the webpage www.optimal-study.nl/tool to use the OPTIModel online. The model can also be used on the site if the app is not downloaded (right part of the screen).

Appendix B. Study protocol for The OPTIMAL Study – a cmRCT

The following description of the prospective OPTIMAL Study is a shortened version of the study protocol as reviewed and approved by the medical ethical committee of the Leiden University Medical Center. The full protocol can be found online at https://clinicaltrials.gov (NCT02705157). The version below focusses on the cohort multiple randomised controlled trial (cmRCT) and why we chose to use this study design for the prospective OPTIMAL Study. Details on data collection, analysis, registration of (serious) adverse events, and data storage can be found in the full protocol.

Cohort multiple randomised controlled trial (cmRCT)

The following paragraphs will portray the difficulties with randomised controlled trials, describe the cmRCT design, discuss our reasons for choosing this design, and explain how we plan to adopt and adjust this design to be applicable in the study population we wish to study and to be feasible as a multicentre study.

Difficulties with RCTs in the palliative setting

Although Randomised Controlled Trials (RCT) are considered to provide high-grade evidence, the classical RCT poses several challenges, especially in pragmatic cancer research. Recruiting sufficient numbers of patients is known to be extremely difficult, not in the least due to cumbersome and time consuming procedures of informed consent, randomization, and inclusion.[1] Furthermore, the mandatory elaborate informed consent for all eligible patients, which is regarded as ethical requirement, is often a barrier for patients to join trials. The abundance of complicated information given combined with the uncertainty of randomization often leads to rejection of participation.[2] Moreover, the recruited (trial) population is often unrepresentative of the reference population, thus leading to poor external validity. It is also possible that patients withdraw from a trial when they do not get the experimental intervention, or exhibit disappointment bias when reporting outcomes. In the

field of oncology, there are often multiple treatments for the same disease, leading to multiple trials for the same population. These all have heterogeneous outcomes and are thus difficult to compare. Finally, modern technology has often surpassed the investigated intervention before the trial has ended.[3]

In the field of palliative medicine, the previously described difficulties become yet more evident. This is not only our personal experience from earlier trials we have performed in the Netherlands, but has also been described in the ZonMw report entitled "Successful inclusion in the palliative setting" (in Dutch: "Succesvol includeren in de palliatieve zorg").[4] This research was performed in response to the observed inclusion problems of studies in the palliative setting. Physical and emotional frailty are two major factors limiting inclusion. Due to physical frailty patients might deny participation; a lack of energy to fill out questionnaires or physically demanding visits at outpatient clinics can be reasons to refuse participation. Emotional frailty is possibly a more important reason for denial of participation, or earlier drop out. The partaking in a research forces a patient to think about his illness in some way or another. This can be extremely confronting, especially if patients have problems coping with their situation. Furthermore, it is plausible that this emotionally unstable situation influences patients in their decision-making. Many patients remain in a state of doubt and have difficulty drawing up the balance, thus being given the choice of participating in randomised research can be very demanding.

Mirroring this emotion is the reserve treating physicians feel to ask their patients to join a study. The physician often does not want to burden the patient any further than the illness already does. The often long and intensive relation between physician and patient further increases this protective attitude.

A more logistical problem with research of patients in the palliative setting is that they are often out of reach of the researchers. The majority of the patients in this phase receives care from their general practitioner or the local hospital, and does generally not visit an academic hospital unless necessary.

The ZonMw report looked into 13 research projects (total budget 2.8 million euro) aimed at improving quality of life and pain of patients in the palliative phase.[4] Four of these studies have been completed, 1 has been discontinued due to inclusion problems, and 1 did not start because the needed sample size was not considered feasible. One of the four completed studies did so on time, 2 were delayed, and 1 changed the aims because the number of patients included could not answer the primary question. All research projects reported problems with inclusion, mainly because too many eligible patients are missed at inclusion. Half of the studies had problems with the inclusion itself, for

example due to certain extra measurements (laboratory analysis) needed for the study or because patients were too ill to think about participation in a trial.

It is thus clear that inclusion in the palliative phase is difficult and although the majority of these limiting factors cannot be changed, they are aspects that need to be taken into account when setting up a new study. The 'cohort multiple randomised controlled trial' design has characteristics that will lessen the burden for the patient and ease the inclusion for the study. Only by employing such a design, will it be possible to answer several pending questions concerning the treatment of patients with bone metastases of the long bones.

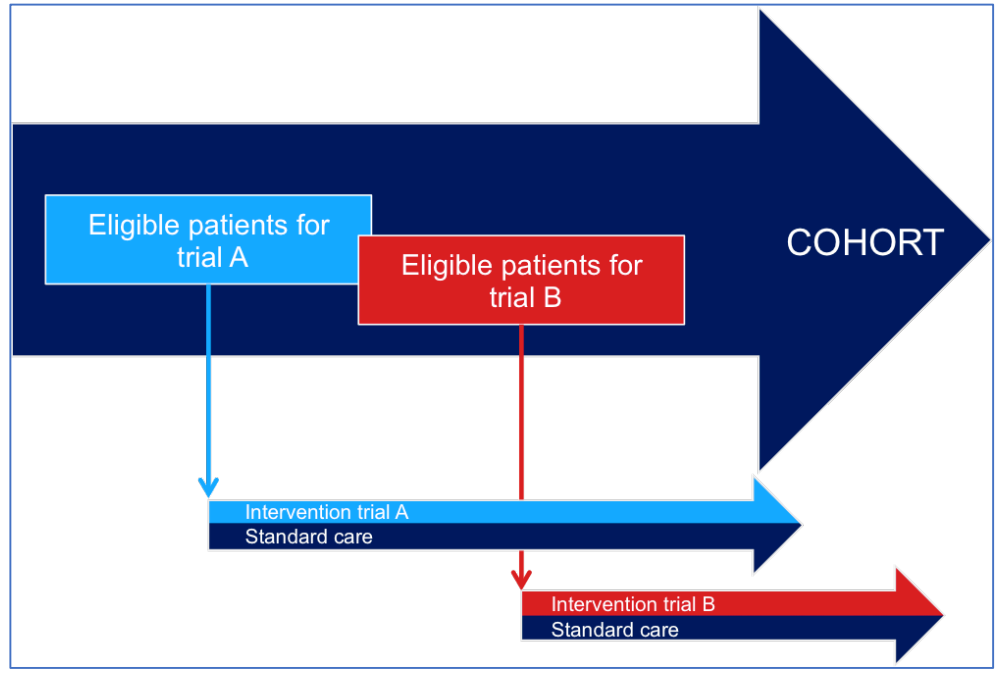

Figure B.1 Cohort multiple randomised controlled trial design.

Cohort multiple randomised controlled trial

In 2010 a new research design, the 'cohort multiple Randmised Controlled Trial' (cmRCT) was developed by Relton et al. in which several solutions are offered for the problems associated with classical RCTs.[5] The backbone of this design is an observational prospective cohort in which patients with the condition of interest (i.e. bone metastases of the long bones) are included (dark blue arrow in figure B.1). These patients are treated according to usual care and baseline data are registered. Secondly, all patients in the cohort are asked to periodically complete questionnaires on the quality of life and pain. Thirdly, patients are

asked for consent to be informed about possible trials in the future. This consent entails permission for random selection if the patient is eligible for a certain trial. For each trial, a random sample is selected from the group of consenting and eligible patients (light blue box in figure B.1), who will be offered the intervention treatment (light blue half of arrow in figure B.1). Only this group will be notified about the trial. After notification follows a second informed consent for participation in the specific trial. If patients do not wish to participate, they will cross over into the 'control group', compromising all patients not randomly selected, and receive standard usual care. The patients who were consenting and eligible but not randomly selected receive standard care as usual without being informed about the trial (dark blue half of the arrow in figure B.1).

Reasons for using this design

With the cmRCT design, patients are not randomized between treatments, but between whether or not they are invited for the intervention arm of a trial. This enables 'patient centred' informed consent: only those patients selected for the intervention arm are offered information about the trial. Thus only these patients are confronted with the possibly difficult choice of participating in a specific trial. Their choice however is a lot clearer than it would normally be, because this group knows that if they consent, they will surely receive the intervention. Likewise, those patients that have not been selected receive straightforward information regarding the standard care only, without any possibly confusing information about a trial.

This aims to replicate 'real world' routine health care, in which patients are only informed about treatments for which they are eligible. This is the keystone aspect of the study design and is of great importance for our potential trial participants who are under substantial emotional stress associated with the end-of-life stage.

It is important to realise that this design is not the same as a Zelen design. The Zelen design randomises patients before a single form of consent has been given. The Zelen design has for that reason been subject to ethical criticisms and is not often applied. In the design we propose, patients are informed on beforehand of the possibility of random selection (when they are eligible for a certain trial), and this will only be performed if the patient consents to that. Patients are clearly informed about the If the patient does not consent, he will receive standard care, i.e. the same care he would have received had there not been a trial.

For the research questions posed in our OPTIMAL study and in the setting we propose to perform our study, there is little room for setting up a traditional RCT. An alternative approach seems to be more appropriate and the outline of the cmRCT design is most suitable. Keystones are the 'patient centred' informed consent and the possibility for multiple prospective trials at the same time. Also, trials will be better comparable and a shorter period of time will be needed for including sufficient amount of patients, thus lowering the costs. Especially in a fragile patient population, such as patients with symptomatic bone metastases, the cmRCT design is uttermost suitable.

Although the clinical experience with cmRTC model is limited, it is currently being used in several studies in the UK, Canada, and The Netherlands [6-8] after ethical approval of respective ethical review committees. In The Netherlands, the University Medical Centre Utrecht (UMCU) is active in the field of further developing the cmRCT design. At their radiotherapy department they currently have 3 cohorts, with each one or more active trials. Their numbers of inclusion into the cohorts, informed consent for notification about trials, and inclusion into trials are promising. Recently, Young-Afat et al. wrote a brief report about their experiences with this new design.[9] They stated that the cmRCT design avoids prerandomization and actively engages participants in the research process during cohort participation. All preparations to employ the cmRCT design in the OPTIMAL Study have been in close collaboration with our colleagues at the UMCU.

Adjustment to the design

There are multiple research questions we wish to investigate and the study design for each trial will differ according to the research question. Therefore, in addition to only performing randomized controlled trials within the cmRCT design, we plan to use different designs, best suitable for each new study. Reasoning for the specific design will be extensively addressed in each separate study protocol.

This small adjustment is necessary, especially, in trials where two or more surgical techniques are going to be compared. Whereas very few eligible patients will be treated in a single year, even the cmRCT design and the multicentre setting can't address this sufficiently.

Thus, some trials will be comparative cohort trials, others pragmatic cluster randomized trials, and some with a cmRCT design. For this reason, we renamed the design: cohort multiple (randomized controlled) trial.

In conclusion, current knowledge concerning adequate, personalized treatment of metastatic lesions of the long bones is insufficient. Several factors of great importance are generally acknowledged: the aim of treatment should be maintaining or improving the quality of life; expected survival is an important factor to bear in mind; and current literature on local treatment modalities is inconclusive. For this reason, it is of upmost importance to explore whether other (innovative) treatments can be an alternative or addition to the current standard treatment options. The OPTIMAL Study, a cohort multiple (Randomised Controlled) Trial accounts for differing life expectancies and focusses on quality of life outcomes. The study will provide high-grade evidence as to which treatment is superior to others.

Objectives

The OPTIMAL Study in its entirety aims to provide a more personalized treatment for metastases in the long bones based on expected survival and impending fracture risk in order to improve functioning and the quality of life for the remaining lifetime in patients with disseminated cancer. The OPTIMAL Study will provide the infrastructure for a prospective cohort (OPTIMAL cohort) and multiple independent trials according to the cm(RC)T design. The specific aims of the cohort are discussed in this protocol.

The primary aim of the cohort is to describe the quality of life and pain perception of patients after local treatment (radiotherapy and/or surgery) of metastases of the long bones, for both the entire cohort as well as for specific treatments separately.

Secondary aims are to describe the complication rate and survival of patients after local treatment (radiotherapy and/or surgery) of metastases of the long bones.

The specific aims of further future individual trials within the cm(RC)T design will be described in separate protocols and submitted to the medical research ethics committee (METC) independently. In general, however, all trials will be pragmatic research trials in search of answers to which treatment (radiotherapy or surgery) fits specific patients (categorised by metastasis location, expected survival and fracture risk) best.

Study design

The OPTIMAL Study encompasses the OPTIMAL cohort and multiple independent trials. The cohort is primarily aimed at collecting patient reported outcomes, but will also provide the facility to select eligible patients for specific

trials according to the cm(RC)T design. This offers the possibility to perform multiple trials at the same time in the same patient population, as shown in figure B.1. Currently one trial is ongoing (the PORT study), the details of which are discussed in a separate protocol. Future trials will also be described in separate protocols, which will be submitted to the medical research ethics committee (METC) independently.

The OPTIMAL cohort

The OPTIMAL cohort is the backbone of the OPTIMAL Study. The cohort will be prospectively collected and multicentre, including all consecutive patients with BMLB who have signed informed consent. These patients will be followed prospectively, and data concerning patient and treatment characteristics as well as patient reported outcomes on quality of life will be collected. Baseline data will be collected by the physician and entered into the OPTIMAL database. These baseline data match the information that is obtained for standard care. For the assessment of patient reported outcomes a set of internationally and nationally validated questionnaires will be used. Further details are discussed in chapter 5. The OPTIMAL cohort will additionally serve as facility for efficient, systematic and simultaneous evaluation of new and existing interventions for bone metastases.

Informed consent

Informed consent will consist of the following three steps.

(1) Participation in the cohort (use and registration of routinely collected clinical data and (possibly) contacting the general practitioner or other physicians involved).
(2) Prospective registration of patient reported outcome measures (quality of life, pain).
(3) Approval to be approached for participating in future (intervention) studies.

Informed consent is signed after full oral and written information has been provided. Consent for step 1 (use and registration of routinely collected clinical data) is mandatory for participation in the OPTIMAL Study. Step 2 is a straightforward consent for receiving and completing questionnaires about patient-reported outcomes. Step 3 is the crux for the 'patient-centred' informed consent. Patients who sign step 3 can be invited to participate in one or more of the studies within the OPTIMAL Study if they meet the inclusion criteria of a certain study and in case of a randomized trial, at random selection, as explained below in figure B.2.

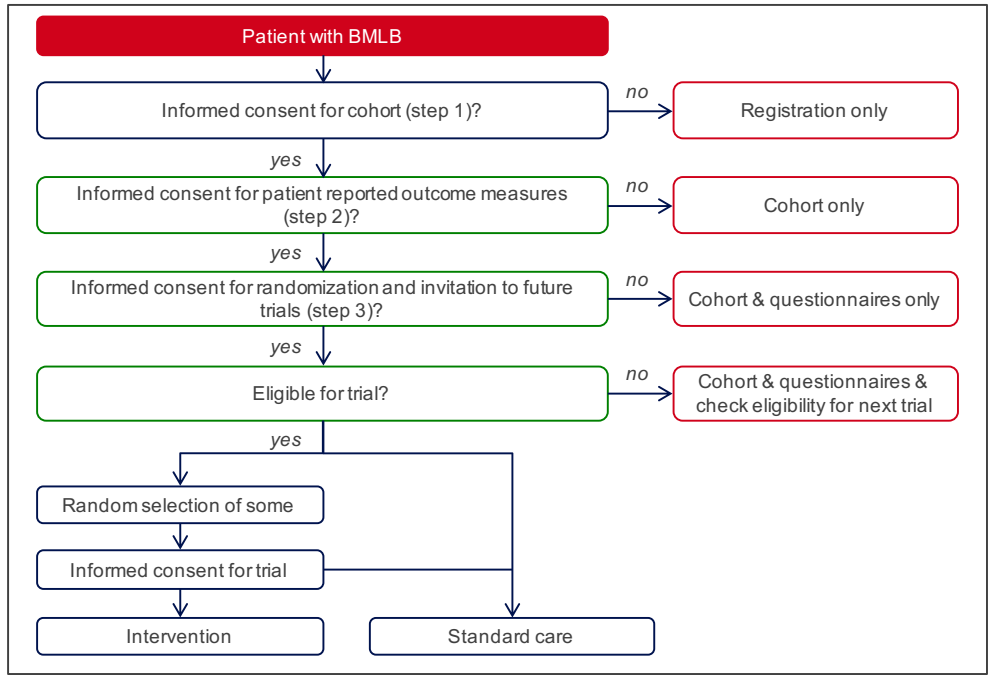

Figure B.2 Flowchart of informed consent.

For a new study, all consenting and eligible (i.e. according to study specific inclusion and exclusion criteria) patients are identified. From this sub-group, in case of a randomized trial, a random selection is made of patients who are invited to participate in the intervention arm. All patients (randomly) selected for the innovative treatment, will receive detailed information about the intervention and the study. Subsequently they may accept or refuse participation (figure B.3).

Those eligible patients who are not randomly selected will receive standard care as usual, without being informed about the randomized trial; this is the essence of 'patient-centred' informed consent.

Consenting to step 3 thus implies permission for being randomly selected to receive information about and be invited for a randomized trial on one hand, and for the use of clinical and self-reported data if patients are eligible but not selected for the intervention arm of a trial on the other hand. Patients are clearly informed that, if they are selected for and invited to the intervention arm of a trial, they are free to refuse it, in which case they will receive standard care. Patients are also informed that if they are not selected, they will be part of the control-arm, and that they therefore may be (temporarily) ineligible for some

future trials. In no case however, will patients be withheld from evidence based standard treatments.

Also, patients participating in in the OPTIMAL Study are permitted to participate in other research (e.g., a 'classic' RCT) outside the OPTIMAL Study.

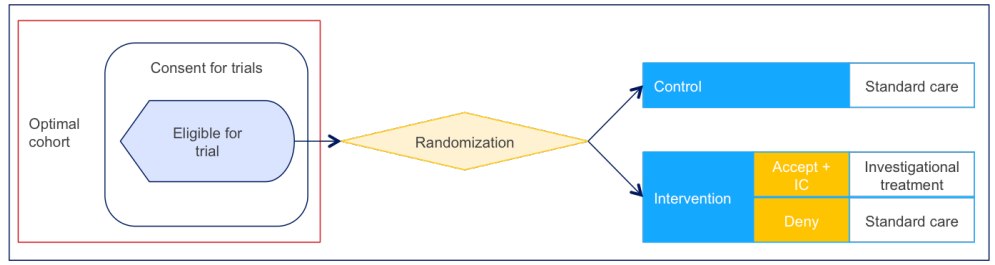

Figure B.3 Schematic overview of process from cohort to trial.

Study population

Population (base)

All patients visiting the radiation oncologist or the orthopaedic surgeon of participating centres, for possible local treatment of a symptomatic BMLB or impending fracture, will be registered in the OPTIMAL registry. This includes patients with newly diagnosed metastatic bone disease as well as patients undergoing re-treatment of the same lesion or patients who have received previous treatment for other lesions.

Inclusion criteria

To participate in the cohort, the patient must meet all of the following criteria:

- Aged 18 or older
- Symptomatic bone metastasis deriving from the bones of the extremities (humerus/femur and further distal) requiring pain medication or intervention with radiotherapy or surgery, or, non-symptomatic bone metastasis with an expected high risk of fracturing requiring treatment
- Radiographic or histologic proof of metastatic bone disease, originating from a solid tumour or primary bone tumour
- Histologic diagnosis of the primary tumour or – if the primary tumour is unknown - at least adequate diagnostic investigations into the origin of the metastasis (e.g. dissemination imaging, histology, biopsy)

Exclusion criteria

A potential patient will be excluded from participation in the cohort if any of the following criteria are met:

- Communication with patient is hampered (e.g. language barrier, severe cognitive impairment, dementia)
- The symptomatic lesion originates from multiple myeloma, solitary plasmacytoma or lymphoma of bone

Note: Previous treatment for metastatic bone disease at the present location is *not* an exclusion criterion.

Methods

Study parameters

At moment of inclusion baseline patient data will be collected for the OPTIMAL cohort, which will also be used for all other studies nested within the OPTIMAL Study. Data will comprehend information concerning demographics (date of birth, gender), medical history (primary tumour, dissemination status), clinical status (systemic treatment) and functioning (Karnofsky performance score, pain score, pain medication). Details concerning the treatment(s) will be reported when relevant.

Patient reported outcome measures

Patients will be invited to fill out questionnaires about pain, quality of life (QoL), and functioning at baseline (pre-treatment; if possible), and 4, 8, 12, and 24 weeks after initial treatment, then every six months for minimal two years or until death. All subsequently or concomitantly symptomatic metastases will be registered (including treatment and follow-up), but a new course of questionnaires will generally not be initiated. These outcome measures will be applied in the entire OPTIMAL cohort. The outcome measures and time-points are the same for all trials within the OPTIMAL Study.

(1) ***Pain*** has been chosen as primary endpoint because it can act as a proxy for mechanical complications (i.e. loosening). Mechanical complications are only relevant for these patients if they give clinical complaints needing treatment.
To measure the primary endpoint patients will be asked to score the worst pain in the past 24 hours on a NRS from 0-10. In addition, patients will be asked to list their usual pain medication and the escape medication they used the previous 24 hours. These questions are derived from the Brief Pain Intervention (BPI) score, which is advised by the International Consensus Statement for Bone Metastasis Research[10]. The BPI is a pain assessment tool for use with cancer patients developed by the Pain Research Group of the WHO Collaborating Centre for Symptom Evaluation in Cancer Care and is also available in Dutch. However, multiple questions are similar to questions in the EORTC QLQ15-PAL and EORTC QLQBM-22 (described below). Thus to spare patients answering the same questions twice, we have selected only 2 questions from the BPI.

(2) ***Quality of life;*** For longitudinal assessment of quality of life after treatment, we will use nationally and internationally used, validated and recommended questionnaires: European Organization for Research and Treatment of Cancer (EORTC) QLQ-C15-PAL[11] and EORTC QLQ-BM22.[12,13] In addition, the EQ-5D questionnaire will be conducted. The EORTC is currently developing a utility scoring instrument for the EORTC QLQ-C30 (from which the QLQ-C15-PAL originates). We expect this scoring instrument will also be applicable for the QLQ-C15-PAL. After validation of this scoring instrument has taken place, we plan to apply it to our data. This would make the addition of the EQ-5D questionnaire redundant and it will then be withdrawn.

(3) ***Function;*** For assessing improvements in functional outcomes after treatment, the Toronto Extremity Salvage Score (TESS) for upper and lower extremities will be used.[14]

Observational clinical data

Observational clinical data will be collected at baseline (pre-treatment; if possible) and at first, and possibly second, post-operative follow-up (generally, patients are subsequently only seen if there are complications or new complaints):

(1) ***Complications;*** For complication rate, the Henderson classification of complications will be applied.[15] This classification identifies five primary modes of endoprosthetic failure: soft tissue failure (type 1), aseptic loosening (type 2), structural failure (type 3), infection (type 4), and tumour progression (type 5). Wound complications with clinical consequences will be registered separately. Re-operations due to complications will be registered as such in the treatment field as a new operation.

(2) ***Radiological status;*** Progression of BMLB will be monitored with conventional radiography and on indication with CT scan. This is according to usual care, generally at six weeks and 3 months. No additional outpatient visits or imaging will be requested for study purposes only. The radiological images will be used to place the subjective reports of pain (as reported by the NRS) into perspective.

(3) S***urvival***; Dates of death will be derived from the Hospital Electronic Patient Registry (in Dutch: Ziekenhuis Informatie Systeem, ZIS), which is linked to the Municipal Personal Records Database (in Dutch: *Gemeentelijke Basisadministratie*, GBA). If this is not possible or not up to date, data will be derived from the general practitioner. The utmost will be tried to prevent sending questionnaires to deceased patients.

References

1. Young RC. Cancer clinical trials--a chronic but curable crisis. *N Engl J Med 2010;363-4:306-9.*

2. Mills EJ, Seely D, Rachlis B, Griffith L, Wu P, Wilson K, Ellis P, Wright JR. Barriers to participation in clinical trials of cancer: a meta-analysis and systematic review of patient-reported factors. *The Lancet Oncology 2006;7-2:141-8.*

3. Relton C, Smith C, Raw J, Walters C, Adebajo AO, Thomas KJ, Young TA. Healthcare provided by a homeopath as an adjunct to usual care for Fibromyalgia (FMS): results of a pilot Randomised Controlled Trial. *Homeopathy 2009;98-2:77-82.*

4. van Gastel W. Succesvol includeren. Mogelijkheden, belemmeringen en risicofactoren. In: ZonMw, ed., 2012.

5. Relton C, Torgerson D, O'Cathain A, Nicholl J. Rethinking pragmatic randomised controlled trials: introducing the "cohort multiple randomised controlled trial" design. *BMJ 2010;340:c1066.*

6. van der Velden JM, Verkooijen HM, Young-Afat DA, Burbach JP, van Vulpen M, Relton C, van Gils CH, May AM, Groenwold RH. The cohort multiple randomized controlled trial design: a valid and efficient alternative to pragmatic trials? *Int J Epidemiol 2017;46-1:96-102.*

7. Burbach JP, Verkooijen HM, Intven M, Kleijnen JP, Bosman ME, Raaymakers BW, van Grevenstein WM, Koopman M, Seravalli E, van Asselen B, Reerink O. RandomizEd controlled trial for pre-operAtive dose-escaLation BOOST in locally advanced rectal cancer (RECTAL BOOST study): study protocol for a randomized controlled trial. *Trials 2015;16:58.*

8. Mayo NE, Brouillette MJ, Fellows LK, Positive Brain Health Now I. Understanding and optimizing brain health in HIV now: protocol for a longitudinal cohort study with multiple randomized controlled trials. *BMC Neurol 2016;16:8.*

9. Young-Afat DA, Verkooijen HAM, van Gils CH, van der Velden JM, Burbach JP, Elias SG, van Delden JJ, Relton C, van Vulpen M, van der Graaf R. Brief Report. *Epidemiology 2016;27-3:389-92.*

10. Chow E, Hoskin P, Mitera G, Zeng L, Lutz S, Roos D, Hahn C, van der Linden Y, Hartsell W, Kumar E, International Bone Metastases Consensus Working P. Update of the international consensus on palliative radiotherapy endpoints for future clinical trials in bone metastases. *Int J Radiat Oncol Biol Phys 2012;82-5:1730-7.*

11. Groenvold M, Petersen MA, Aaronson NK, Arraras JI, Blazeby JM, Bottomley A, Fayers PM, de Graeff A, Hammerlid E, Kaasa S, Sprangers MA, Bjorner JB, Group EQoL. The development of the EORTC QLQ-C15-PAL: a shortened questionnaire for cancer patients in palliative care. *Eur J Cancer 2006;42-1:55-64.*

12. Chow E, Bottomley A. Understanding the EORTC QLQ-BM22, the module for patients with bone metastases. *Expert Rev Pharmacoecon Outcomes Res 2009;9-5:461-5.*

13. Zeng L, Chow E, Zhang L, Tseng LM, Hou MF, Fairchild A, Vassiliou V, Jesus-Garcia R, Alm El-Din MA, Kumar A, Forges F, Chie WC, Bedard G, Bottomley A. An international prospective study establishing minimal clinically important differences in the EORTC QLQ-BM22 and QLQ-C30 in cancer patients with bone metastases. *Support Care Cancer 2012;20-12:3307-13.*

14. Willeumier JJ, van der Wal CWPG, van der Wal RJP, Dijkstra PDS, Vliet Vlieland TPM, van de Sande MAJ. Cross-Cultural Adaptation, Translation, and Validation of the Toronto Extremity Salvage Score for Extremity Bone and Soft Tissue Tumor Patients in Netherlands. *Sarcoma 2017;2017:1-6.*

15. Henderson ER, Groundland JS, Pala E, Dennis JA, Wooten R, Cheong D, Windhager R, Kotz RI, Mercuri M, Funovics PT, Hornicek FJ, Temple HT, Ruggieri P, Letson GD. Failure mode classification for tumor endoprostheses: retrospective review of five institutions and a literature review. *J Bone Joint Surg Am 2011;93-5:418-29.*