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Health informatics — Datasets and data structure for clinical and biological evaluation metrics in radiotherapy

Informatique de santé — Jeux de données et structure de données pour les métriques d'évaluation clinique et biologique en radiothérapie

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Foreword

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This document was prepared by Technical Committee ISO/TC 215, *Health informatics*.

Any feedback or questions on this document should be directed to the user's national standards body. A complete listing of these bodies can be found at www.iso.org/members.html.

Introduction

Radiotherapy or radiation therapy is a treatment method used mostly in cancer care. Due to rapid technical advances of the radiotherapy treatment modalities, it is becoming increasingly important to select an appropriate radiotherapy treatment modality for individual patients by considering patient conditions and the resources that are required.

In the case of external-beam radiation therapy (EBRT), where the therapeutic radiation beams are emitted from a machine outside the body of the patient, treatment planning is performed prior to treatment. When selecting a treatment modality from among possible candidates, treatment plans are made for the candidates, if necessary, and then the dosimetric indices and/or radiobiological metrics corresponding to the treatment plans are compared.

Tumour control probability (TCP) and normal tissue complication probability (NTCP) are among the metrics used in the comparisons. They are simple phenomenological models based on clinical observations which are described in ICRU 83[12] as clinical and biological evaluation metrics (CBEMs), along with other metrics such as equivalent uniform dose, conformity and homogeneity indices. Recently, more sophisticated models incorporating non-dosimetric patient factors, spatial dose metrics and -omics elements (e.g. radiomics and proteomics) have also received attention and some of them are starting to be referred to in clinical trials in some countries.

For wider and safer use of CBEMs in clinical practice and clinical trials, it is important to provide an effective framework for ensuring the traceability of calculated metrics. Standardization of data formats for reporting calculated CBEMs is one possible way. However, no attention has been paid to such standardization to date, while there is active research on new metrics or new models as well as increasing attention to transparent reporting of developed models.

This document describes datasets and data structure for the reporting of CBEMs, especially of simple model types of TCP and NTCP. Scientific aspects of reliability of CBEMs are not in the scope of this document. Because of the variety of CBEM models, when an evaluated CBEM is to be reported and/or referred to, it is important to report and/or refer to the value of the calculated CBEM along with information about the CBEM model itself as well as with dose information and non-dosimetric factors of the patient that are used in the calculation. It is also important to include descriptions about uncertainties, underlying assumptions, limitations and situations for application of the CBEM model. In general, the dose information of the treatment plan used in the calculations (dose-volume histogram (DVH) in most cases) is converted to match the model definition; for instance, adjusting the differences in fraction size between the plan of the patient and the reference fraction size of the CBEM model. This means that the apparent values of the doses (e.g. maximum dose and mean dose) used in the calculation are CBEM-model-specific. To ensure traceability, inclusion of the description about the process of such dose conversions along with the value of the representative dose values would be a great help. This document provides datasets and data structure for CBEM reporting by considering the above mentioned aspects.

While this document is not intended to cover the reporting of CBEMs by contemporary sophisticated models, the data structures described in this document can apply to the reporting of them as well.

Health informatics — Datasets and data structure for clinical and biological evaluation metrics in radiotherapy

1 Scope

This document reports on the datasets and a data structure for reporting clinical and biological evaluation metrics (CBEMs). The reporting of radiation dose estimates is outside the scope of this document.

This document is applicable to CBEMs for external-beam radiation therapy (EBRT) modalities, but not CBEMs for brachytherapy or molecular radiotherapy.

Various types of radiotherapy treatment modalities are available for cancer care. Consequently, there is a growing awareness of the need for objective schemes that will contribute to enable the selection of an appropriate radiotherapy treatment modality for individual patient. The use of CBEMs, the metrics associated with a certain radiotherapy treatment plan for a patient, is attracting attention for clinical purposes in the field of EBRT. In anticipation of the clinical use of CBEMs, the importance of research on clinical and scientific aspects of CBEMs is increasing, in concert with the importance of establishing a standardized data format for reporting of specifics of a CBEM.

2 Normative references

There are no normative references in this document.

3 Terms and definitions

For the purposes of this document, the following terms and definitions apply.

ISO and IEC maintain terminology databases for use in standardization at the following addresses:

— ISO Online browsing platform: available at https://www.iso.org/obp

— IEC Electropedia: available at https://www.electropedia.org/

3.1
data element
unit of data that is considered in context to be indivisible

Note 1 to entry: The definition states that a data element is "indivisible" in some context. This means it is possible that a data element considered indivisible in one context (e.g. telephone number) can be divisible in another context (e.g. country code, area code, local number).

[SOURCE: ISO/IEC 11179-1:2023, 3.3.4, modified — Example deleted.]

3.2
Digital Imaging and Communications in Medicine
DICOM
standard for the communication and management of medical imaging information and related data

Note 1 to entry: The DICOM Standard facilitates interoperability of medical imaging equipment.

Note 2 to entry: DICOM is defined in ISO 12052.

[SOURCE: ISO/IEC 39794-16:2021, 3.16]

3.3
dose fractionation
method of administration of radiation in which the absorbed dose is divided into two or more fractions separated in time

[SOURCE: IEV ref 881-11-18]

3.4
dose-volume histogram
DVH
dose as a distribution-function or frequency-function over a specified volume

[SOURCE: ICRU 50, modified — Abbreviated term "DVH" added.]

3.5
endpoint
<primary> principal indicator(s) used for providing the evidence for clinical performance, effectiveness or safety in a clinical investigation

[SOURCE: ISO 14155:2020, 3.22]

3.6
intensity-modulated radiation therapy
IMRT
treatment procedure requiring, in general, the coordinated control of photon or electron fluence, beam orientation relative to the patient, and beam size of the external beam, either in a continuous or a discrete manner, and as pre-determined by a *treatment plan* (3.12)

Note 1 to entry: The primary purpose of IMRT is to improve the conformity of the dose distribution to the planned target volume, while minimizing dose to surrounding healthy tissue.

[SOURCE: IEC 60976:2016, 3.2.7]

3.7
numerical value equation
numerical quantity value equation
mathematical relation between numerical quantity values, based on a given quantity equation and specified measurement units

[SOURCE: ISO/IEC Guide 99:2007, 1.25, modified — Examples deleted.]

3.8
radiotherapy
radiation therapy
therapy that uses ionizing radiation to kill cells and shrink pathological tissues

Note 1 to entry: Radiation may be delivered by a machine outside the body (external-beam radiation therapy), or it may come from radioactive material placed in the body near cancer cells (brachytherapy) or from radiopharmaceutical administered to the patient (molecular radiotherapy).

[SOURCE: ISO 12749-6:2020, 3.3.2]

3.9
radiotherapy treatment planning system
RTPS
device, usually a programmable electrical medical system including its associated peripherals, that is used to simulate the application of radiation to a patient for a proposed radiotherapy treatment

Note 1 to entry: It usually, but not necessarily, provides estimations of absorbed dose distribution in human tissue using a particular algorithm or algorithms. These algorithms provide simulations of radiation that is typically from, but not necessarily limited to, medical electron accelerators, gamma beam therapy equipment, or in brachytherapy from radioactive sources.

[SOURCE: IEC 62083:2009, 3.1.6]

3.10
region of interest
ROI
sub-dataset picked out from the entire dataset for a specific purpose

[SOURCE: ISO 20263:2017, 3.1.24]

3.11
relative biological effectiveness
RBE
<of radiation> ratio of the absorbed dose of a reference radiation to the absorbed dose of the radiation of interest, generally X-ray or gamma ray, that produces the same level of biological effect

Note 1 to entry: The term should only be used in radiobiology.

[SOURCE: IEV ref 881-17-03]

3.12
treatment plan
all patient and dosimetric information that is intended for use by appropriately qualified persons for the purpose of prescribing or administering *radiotherapy* (3.8), including any information to be transmitted to other equipment

Note 1 to entry: A printed or plotted treatment plan is referred to as a treatment plan report.

[SOURCE: IEC 62083:2009, 3.1.8]

3.13
treatment planning
process of establishing the *treatment plan* (3.12)

[SOURCE: IEC 62083:2009, 3.1.9]

4   Abbreviated terms

CBEM   clinical and biological evaluation metric

CI   confidence interval

DICOM   Digital Imaging and Communications in Medicine

DVH   dose-volume histogram

EBRT   external-beam radiation therapy

IMRT   intensity-modulated radiation therapy

LOINC   Logical Observation Identifiers Names and Codes (Regenstrief Institute, Inc.)

NTCP   normal tissue complication probability

RBE   relative biological effectiveness

ROI   region of interest

RTPS   radiotherapy treatment planning system

TCP   tumour control probability

5   CBEMs in EBRT

5.1   General

EBRT is a form of radiotherapy for delivering a beam or beams of ionizing radiation from outside the body of patients. There are several different types of modalities of EBRT (EBRT modality) regarding beam types and ways of forming dose distributions in the patient body, each provided by a specific device or system. For specific patients, a suitable EBRT modality is selected among those available by considering the patient condition and the resources required. Recently, the use of CBEMs for treatment plans of EBRT has been gaining attention in clinical practice and for research purposes.

5.2   CBEMs

In ICRU 83[12], the concept of CBEM is described in the section of "Level 3 Reporting" for intensity-modulated radiation therapy (IMRT). IMRT is one EBRT modality, however, the described concept of the CBEM can also be applicable to other EBRT modalities. In ICRU 83[12], TCP, NTCP and combination metrics of TCP and NTCP are described. This document examines TCP and NTCP as CBEMs but does not examine combination metrics of these two.

The CBEM is a metric which is associated with a treatment plan. Multiple CBEMs can be associated with one treatment plan, e.g. on metrics for different endpoints and/or by different CBEM models.

A schematic figure of the calculation process of a CBEM is shown in Figure 1. A CBEM is calculated using a CBEM model which is expressed as one or multiple numerical value equations. The input to the equations is the radiation dose information of a region of interest (ROI) for a treatment plan, which corresponds to the definition of the CBEM model. In particular cases, it can be multiple ROIs. If the model requires information regarding patient factors, this is also input for the calculations.
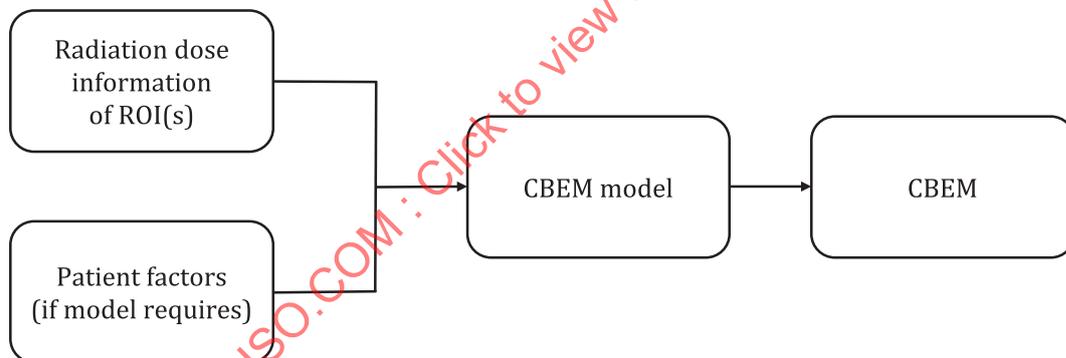

Figure 1 — Schematic of the CBEM calculation process

When the type of a CBEM is TCP, the ROI is the tissue volume that contains the tumour to be treated, depending on the definition of the TCP model. When the type of a CBEM is NTCP, a ROI is one or plural of normal tissues near the tumour. Radiation dose information of a ROI typically is either of the DVH, or one or more dose-volume indices specific to the CBEM model. Examples of such values include average doses, maximum doses or indices calculated from the DVH.

Before being input in the CBEM calculations, it is necessary to consider conversion of radiation dose information (dose conversion) under appropriate assumptions. Examples of such considerations include but are not limited to dose conversions in relation to the differences in radiation beam types and treatment schedules (number of fractions and prescription doses per fraction) between the target plan for the CBEM calculations and plans used for participants in the CBEM model development study. Scientific aspects of dose conversions are not covered in this document, however, data elements for narrative descriptions of assumptions in connection with dose conversions are provided in the datasets described in this document.

Examples of patient factors for CBEM calculations include information related to age, sex, diagnostics of the disease and pre-treatment health conditions. In most cases, these are treated as dummy variables (i.e. 0 or 1) in the calculations of the CBEMs.

5.3 Use case of CBEMs

5.3.1 Selection of the EBRT modality

An example of the workflow for selecting an EBRT modality for a specific patient by referring CBEMs is shown in Figure 2. For the patient, treatment plans for two candidate modalities A and B are generated by qualified persons such as physicians and medical physicists, by using different radiotherapy treatment planning systems (RTPSs). Information of the treatment plans is stored in the RTPS as electronic files. The information for this can be assessed by a CBEM calculation device through the file server functions of the RTPS.

For the two treatment plans, CBEMs, namely TCP and NTCP, are calculated by a qualified person using the CBEM calculation device. Through the graphical user interface of the CBEM calculation device, the qualified person(s) carefully selects the CBEM models suitable for the patient and the treatment plans, and then performs dose conversions by considering assumptions based on relevant aspects. The calculated results of the TCPs and NTCPs are stored as electronic files, as CBEM reports for the respective treatment plans. In the CBEM reports, the detailed information of the used models, the underlying assumptions of the models, information of the treatment plans, assumptions and adopted schemes for dose conversions, and some patient factors are included.
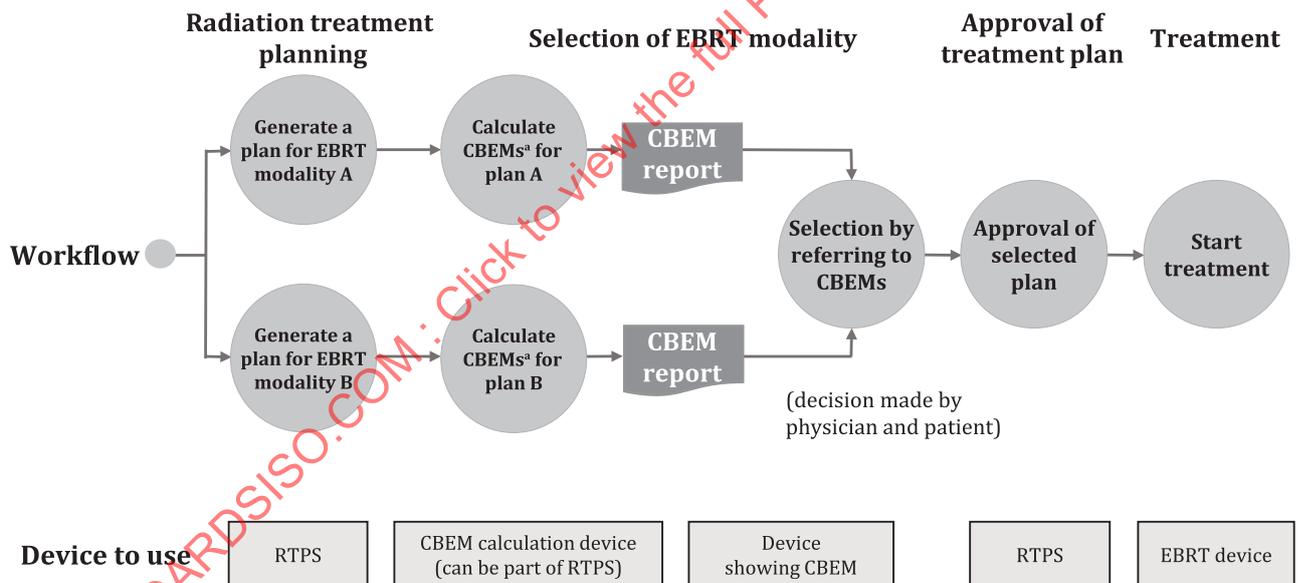
a CBEMs: TCPs and NTCPs about different complications. The same CBEM models are used for both treatment plans.

Figure 2 — Use case of CBEMs in the selection of an EBRT modality for a patient

Then the information in the CBEM reports for the two treatment plans are shown through a CBEM referring device by the same or different qualified person(s), possibly with the patient, to decide which EBRT modality or treatment plan to select. The selected treatment plan is approved, and it is used for the treatment.

5.3.2 Clinical trials

In clinical trials, CBEMs can be used to stratify patients into different risk groups, reduce the bias related to the type of EBRT and improve objectivity. However, before using the CBEMs for these purposes, it is

important to conduct appropriate quality assurance of the models by assessing the uncertainties and limitations of the models.

5.4 Existing data format for CBEMs

There is no existing standard regarding data format for reporting CBEMs.

6 Datasets and data structure for a CBEM

6.1 General

This document illustrates a general figure of datasets and a data structure for reporting typical CBEMs. Any specific data format is not assumed, however, available existing codes corresponding to some data elements are shown in in Tables 2 to 5. In this document, it is assumed that a data object for CBEMs is stored in an electronic file, a CBEM report, although this is not always be the case. A CBEM is associated with a treatment plan of a patient. The datasets and the data structure described in this document allow for multiple CBEMs in one CBEM report or kept in separate CBEM reports.

6.2 Datasets and data structure

6.2.1 Structure of the CBEM report

A CBEM report consists of a header part and a body part. The header part includes document identification information, author information and patient information. The patient information includes patient ID, patient name, sex, date of birth, address, telephone number and other particulars. The body part includes CBEM-specific information. This document describes datasets and format of the body part.

6.2.2 Structure of the body part

The structure of the body part of the CBEM report is shown in Table 1. Data elements included in each section are shown in Tables 2 to 5.

Table 1 — Structure of the body part of a CBEM report

Sections	Card	Description
Patient condition information	1..1	Includes patient information related to the calculation of CBEMs and the selection of CBEM models (see Table 2).
Treatment plan information	1..1	Includes data elements of the target radiotherapy treatment plan of the CBEM calculation, as well as information on planned combination therapies (see Table 3). Data elements associated with calculated CBEM-model-specific radiation dose information are not included in this section but in the next section.
CBEM information	1..*	Includes calculated results of CBEMs, information on the CBEM models (source of the model, parameters of the model, uncertainties and limitations of the model, etc.) and data elements associated with calculated CBEM-model-specific radiation dose information (see Table 4).
Comments on CBEM report	0..1	Comments on the CBEM report file (see Table 5).
NOTE In this table and Tables 2 to 5, "card" (or cardinality) is the number of occurrences. The format is $m..n$, where m is the minimum of occurrences and n is the maximum number of occurrences.		

6.2.3 Patient condition information

The details of the "patient condition information" section includes the elements in Table 2. Information on existing LOINC and DICOM codes for data elements are also listed.

"Patient ID in treatment plan data" and "Patient name in treatment plan data" corresponds to data elements recorded in the treatment plan used for the CBEM calculation. These items are used to confirm that the treatment plan is for right patient and correspond to the patient information in the header.

"Patient factors used in CBEM calculation" corresponds to input for the CBEM calculation. Examples include age at the beginning of the treatment, sex, pre-treatment health conditions and others.

"Patient factors related to CBEM model selection" corresponds to information regarding selection of the CBEM model used for the calculations. It is typically helpful when the CBEM model being used was developed from sub-group analyses.

Table 2 — Patient condition information

Elements	Card	Description	Existing code
Patient ID in treatment plan data	1..1	Patient ID recorded in the treatment plan data for the CBEM calculation.	LOINC 76435-7 DICOM Patient Module (0010,0020)
Patient name in treatment plan data	1..1	Patient name recorded in the treatment plan data for the CBEM calculation.	LOINC 54125-0(Nom) DICOM Patient Module (0010,0010)
Patient factors used in CBEM calculation	0..*	Set of labels, values, and comments. Example: [Age over 70 or less, 1, 73yr].	—
Patient factors related to CBEM model selection	0..1	Narrative description related to the selection of the CBEM models.	—

6.2.4 Treatment plan information

The "treatment plan information" section includes the elements in Table 3. Information on existing LOINC and DICOM codes for data elements is also listed.

Table 3 — Treatment plan information

Elements		Card	Description	Existing code
Radiotherapy		1..1	Information on the planned radiotherapy.	—
	Reference Object	1..1	Identification of the source of radiation dose information used for the CBEM calculations.	DICOM RT Dose Module (300C,0002)
	Plan creation date and time	1..1	Date and time the treatment plan was created.	DICOM SOP Common Module (0008, 0012), (0008,0013)
	Radiation type	1..1	Information about the radiation beam type assumed in the treatment plan.	DICOM RT Beams Module/RT Ion Beams Module (300A,00C6)
	Target prescription dose	1..1	Value and unit of prescription dose in the treatment plan.	LOINC 21958-4 DICOM RT Prescription Module (300A,0026)
	Number of fractions	1..1	Number of fractions of the treatment plan.	LOINC 21959-2 DICOM RT Fraction Scheme Module (300A,0078)
Combination therapy		1..1	Information on planned combination therapies.	LOINC 22040-0

6.2.5 CBEM information

The "CBEM information" section includes the elements in Table 4. Information on existing LOINC and DICOM codes for data elements are also listed. In this table, data elements are structured so that the used CBEM model and the process of the CBEM calculations can be traceable even in cases when

multiple CBEMs are reported in a single CBEM data file or multiple dose-volume indices of one or plural of ROI are used for a single CBEM calculation. Given the importance of assessing uncertainty, limitations and situations for application of the model in the use of CBEM, data elements regarding them are also included in this table.

Table 4 — CBEM information

Elements	Card	Description	Existing code
CBEM summary	1..*	Summary of the evaluated CBEM.	—
CBEM number	1..1	Ordinal number of the CBEM summary in the CBEM document.	—
Type of the CBEM	1..1	TCP or NTCP.	—
Name of the endpoint (short)	0..1	Name of the endpoint of the CBEM (short).	—
Name of the endpoint (long)	1..1	Name of the endpoint of the CBEM (long).	—
Result of CBEM	1..1	Calculated value, unit and confidence interval (CI) (optional) of the CBEM.	—
CBEM model and dose information	1..1	Information of the CBEM model itself and data elements on CBEM-model-specific radiation dose information used for the CBEM calculation.	—
Model identifier	0..1	Information to identify CBEM model (code and system code when available).	—
Information source of CBEM model	1..1	Information source of the CBEM model (article reference information and/or web addresses).	LOINC 48766-0
Limitations and applicable situations of the CBEM model	1..1	Description regarding limitations and situations for application of the CBEM model.	—
CBEM model equation type	1..1	Model equation type of the CBEM (e.g. LKB, Lyman, Logistic Regression Model, …, other).	—
Reference fraction size of CBEM model	1..1	Value and unit of the prescription dose per fraction assumed in the CBEM model. Additional descriptions/details are needed for some cases.	—
Reference RBE of CBEM model	1..1	Description of the relative biological effectiveness of the CBEM model (to X-Ray) and/or assumptions.	—
CBEM model parameters	1..*	Lists of CBEM model parameters [parameter name, ROI label (optional), value, unit (optional), CI (optional)].	—
Variance-covariance matrix of model parameters	0..1	Variance-covariance matrix of the CBEM model parameters. Lists of [name of a parameter, list of values].	—
Other assumptions of CBEM model	0..1	Assumptions in the CBEM model other than listed above. Can include information for dose conversion among plans of participants in the CBEM model development study when the dose fractionations differ among them.	—
Summary of CBEM model development study	0..1	Summary of the CBEM model development study. Can include sample size, eligibility of participants, validation scheme and others.	—
CBEM-model-specific radiation dose information	1..*	Data elements on the CBEM-model-specific radiation dose information used for the CBEM calculation of the target treatment plan.	—

Table 4 *(continued)*

	Elements	Card	Description	Existing code
	ROI number	1..1	Information to identify ROI used for the calculation of the CBEM for the target treatment plan data.	DICOM Structure Set Module (3006, 0022)
	ROI name	1..1	Information of the name used for the calculation of the CBEM.	LOINC 20298-6 DICOM Structure Set Module (3006, 0026)
	Dose conversion information	1..1	Description regarding conducted dose conversion to fit to the CBEM model. Can include information regarding dose fractionation and relative biological effect.	—
	Dose-volume index used in CBEM calculation	0..*	List of [name (e.g. mean dose, maximum dose, equivalent uniform dose, volume ratio), corresponding ROI label in CBEM model parameters (when multiple dose values are input for the CBEM calculation), value, unit].	—

6.2.6 Comments on CBEM report

"Comments on CBEM report" section includes the elements in Table 5. Information on the existing LOINC code is also listed here.

Table 5 — Comments on CBEM report

Elements	Card	Description	Existing code
Report comment	0..1	General comments for the CBEM report.	LOINC 86467-8

Annex A
(informative)

Example of a CBEM model and related data elements

A.1 General form of CBEM models

A numerical value equation for CBEM models can be expressed as:

CBEM = $F(D, P \mid \beta)$

where

    D is the dose information to an ROI of a treatment plan to be used for the CBEM calculation;

    P are the patient factors or corresponding numerics to be used for the CBEM calculation;

    β are the model parameters specific to the CBEM model.

The D typically is a dose-volume index to a ROI (e.g. mean dose [GyE], maximum dose [GyE], volume ratio under a certain dose level [%]), or a DVH. In particular cases, CBEM models can require multiples of dose information for one or different ROIs.[13]

The P is required as input in some cases of CBEM models, while often it is not required. For example, CBEM models of multivariable regression models usually require some numerical input related to patient factors. Most of such numerical input data are dummy variables. Examples include: age at the beginning of the treatment is over 70(1) or not (0), male (1) or female (0), viral hepatitis positive (1) or negative (0), and others.

A.2 Example of a CBEM model

The Lyman-Kutcher-Burman (LKB) model is one of most common types of CBEM models. It is often used for NTCP models, which have the numerical value equations given by

$$\text{NTCP} = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{t} \exp\left(-\frac{x^2}{2}\right) dx$$

$$t = \frac{gEUD - TD_{50}}{m \times TD_{50}}$$

$$gEUD = \left(\sum_i v_i D_i^{\frac{1}{n}}\right)^n$$

where

    $gEUD$ (generalized equivalent uniform dose) is "the dose that, if given uniformly to the entire organ, is believed to yield the same complication rate as the true dose distribution"[14];

    TD_{50}, m and n are model parameters (β) determined through clinical observations;