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Project Plan for the CEN Workshop on NOVEL METHODS FOR ISOLATING WEAR PARTICLES FROM JOINT REPLACEMENTS AND RELATED DEVICES AND FOR EVALUATING THEIR BIOLOGICAL IMPACT IN VITRO (CEN/WS 87)

(approved during the CWA Kick-off meeting on 2017-06-15)

1. Status of the Project Plan

Project Plan, approved at the CWA Kick-off meeting.

2. Background to the Workshop

The market environment

Articulating human joint replacements currently constitute a global market exceeding €14 billion p.a. that is expected to rise as demographics reflect an ageing population. However, faster growth has been seen in the revision market, where prosthetic joints are replaced, than in primary interventions. The major cause of these revisions is that all joint replacements are prone to wear leading to loss of implant function. Furthermore, it has been demonstrated that adverse or extreme loading has a detrimental effect on implant performance. Thus, device failure still occurs too frequently, leading to the conclusion that their longevity and reliability must be improved. Whilst improvements can result from improved clinical practice (many failures are directly attributable to imprecise or inadequate surgical procedures), improvements in resistance to wear and mechanical damage of the articulating surfaces offers a means of addressing many of the failures observed.

Whilst an improved wear resistance from, for example, the application of a hard surface coating to articulating elements might enhance device longevity, such devices will, in the future, likely only achieve the necessary regulatory approval if, amongst other requirements, the nature, volume, morphology and biological impact of wear debris generated during the anticipated functional life of the implant is quantified. Such quantification is typically done on the basis of short to medium term simulator studies, performed according to international norms, from which the wear debris generated per million cycles is isolated and its biological impact evaluated. Such evaluation is typically undertaken using cytotoxicity assays, such as those that require conversion of a substrate by live cells to effect a colour change or produce light that can be quantified, e.g. MTT assay. However, cytotoxicity is a “blunt” tool, where cells are assessed as either alive or dead, whereas, some cells might undergo other damage such as DNA damage or

oxidative stress (production of reactive oxygen species), which, while not immediately cytotoxic, could accumulate over time causing adverse future events such as tumour formation.
In addition, it is noted that there might be a synergistic effect of inflammation in response to the particles, which lower local pH accelerating corrosion and ion release, leading to increased toxic responses. However, as surfaces become more wear resistant the amount of debris generated per unit time will reduce, making its isolation, characterisation and impact evaluation more and more challenging as the wear resistance increases.

The Workshop will introduce:

1. a new method for isolating wear particles generated from extremely low wearing surfaces of implantable devices not amenable to existing international protocols, e.g. ISO 17853:2011; and

2. a novel, tiered approach to the in vitro assessment of the biological impact of such wear particles based on a number of existing methodologies.

The legal environment (Directives and relevant national legislation)

Human joint replacements are the subject of different legislative requirements in different market jurisdictions. For example, in the European Union these devices are covered by the Medical Devices Directive 93/42/EEC and subsequent amendments, and are regulated by the relevant national notified bodies. In the USA, medical devices are regulated by the Food and Drug Administration (FDA) under the USA FDA medical devices regulations. In Japan such devices are regulated by the Japan medical device regulations. Whilst other regulatory systems exist, these three regulatory frameworks and requirements essentially cover all national and international requirements for replacement articulating joints. Although requirements differ between the different systems, all systems have certain requirements in common, such as the need for pre-clinical biological and mechanical testing of devices prior to implantation, with such testing typically being specified by existing international (ISO and ASTM) and/or regional (CEN) standards.

Thus amongst other testing, new articulating human joint replacements are subject to wear testing according to, e.g. ISO 14242-2, *Implants for surgery – Wear of total hip-joint prostheses – Part 2: Methods of measurement*, with any wear debris generated being isolated and characterized according to ISO 17853, *Wear of implant materials – Polymer and metal wear particles – Isolation and characterization*. Additionally, new articulating human joint replacements are subject to biological evaluation according to specified parts of EN ISO 10993, *Biological and clinical evaluation of medical devices*. However, whilst EN ISO 10993 specifies biocompatibility testing in vitro through direct and indirect culture with fibroblast (L929 mouse fibroblasts) or BHK cell lines, it makes no reference to particulates, and no reference to the cells most relevant to implant failure, e.g. mononuclear cells, which have been shown to play a key role in osteolysis and failure of implanted joint replacements.

Existing standards and standard-related activities and documents

In the area of wear particle isolation, the subject of one of the two proposed CWA outputs from the Workshop, the only existing international standard, developed by ISO/TC 150/SC4, *Implants for Surgery – Bone and joint replacements*, is ISO 17853:2011, *Wear of implant materials – Polymer and metal wear particles – Isolation and characterization*, referred to within the legal environment section of this project plan. However, whilst the procedures in this standard are relevant to the isolation of wear debris from relatively high wearing couples, such as metal on polymer, they are of limited or no value for use with low wearing couples, such as modern zirconia toughened alumina (ZTA) ceramic-on-ceramic implants. Given the need for the introduction of implant systems with reduced wear, it is clear that other, more powerful techniques, are required for the isolation of wear debris in such cases; however ISO/TC 150/SC4 currently has no deliverable related to the proposed CWA outputs in its work programme.

In the case of the in vitro evaluation of the biological impact of wear particles (which is the subject of the second proposed output from the Workshop), the principal standards relevant to such evaluation are within the EN ISO 10993, *Biological and clinical evaluation of medical devices* series, as mentioned within the legal environment section. However, this set of approximately 20 standards and support documents is, by necessity, generic in nature and contains few requirements specific to any particular device. The set of standards rather provides a framework or a scheme for testing different devices, which requires informed decisions to be made in a series of steps leading to the selection of the most appropriate tests.

Motivation for the creation of this Workshop

The European Commission's FP7 RTD project 'LifeLongJoints' is engaged in developing a new ceramic coating system for use in hip prostheses, including articulating surfaces and tapers, which will have very low wear and for which the wear particles, when produced, will be both bio-resorbable, and biocompatible, thus helping to overcome issues associated with debris induced osteolysis, metallosis and pseudo-tumours. Because of the anticipated low wear rate of this new coating, along with the dissolution profile of the wear particles produced, it has been necessary to develop new wear particle isolation procedures that will allow the collection and subsequent biological testing of wear debris from joint simulator and reciprocating wear testing under joint relevant conditions. The new method appears to be 10 to 100 times more sensitive than other protocols, is easier to carry out, less complicated and cheaper than competing methods and, as such, represents an important advance in the protocols available for wear debris isolation. In addition to its use for isolating wear debris generated by joint replacements, it aims also to be applicable to the isolation of such debris generated in related devices, e.g. debris resulting from fretting wear between fracture repair plates and the pins holding them in place. This new protocol will form one of two CEN Workshop Agreement (CWA) outputs delivered by the Workshop.

In order to evaluate the benefits of the new ceramic coating a tiered approach to the in vitro evaluation of biological impact of the wear particles has been developed which represents a valuable advance on the use of a series of specific tests. Currently the biological responses to wear particles are assessed either by measuring inflammatory mediators (cytokines), e.g. for

responses to UHMWPE particles, or by measuring cytotoxicity of particles, e.g. to CoCr particles from metal-on-metal implants. Here, the proposal is to assess biological responses more holistically, considering inflammatory cytokine release, cytotoxicity, genotoxicity, oxidative stress and membrane toxicity to ensure maximum information is generated for the particles under evaluation. The proposed protocol, which it is anticipated will provide the second of the two outputs from the Workshop, makes use of a number of established methodologies, but deviates from normal practice by combining them into a toolkit of tests that provides a significantly more relevant, and complete measure of biological impact. As with the particle isolation protocol, it is anticipated that the new 'toolkit' will also be suitable for evaluating the biological impact of wear debris from other, related implant devices.

The motivation behind the Workshop is to disseminate the two new protocols to current practitioners in the field and to encourage them to evaluate these in a carefully structured way in order to establish their repeatability and reproducibility in preparation for the development of formal standards. The use of the CEN Workshop Agreement format will allow the new methods to receive the widest possible dissemination to, and evaluation by, relevant stakeholders so that all practitioners, and not just those involved in formal standardization, can learn of, and contribute to, their further development.

3. Workshop proposers and Workshop participants

The Workshop is proposed by the LifeLongJoints EU project (www.lifelongjoints.eu), represented by Professor Joanne Tipper, from the Institute of Medical & Biological Engineering in the University of Leeds, who is proposed as Chair of the Workshop. Numerous relevant individuals and companies will be identified and invited to register to the Workshop.

4. Workshop scope and objectives

Scope

To provide a forum for the wide-scale dissemination, discussion, critical evaluation, optimization and implementation of new protocols for wear particle isolation from low wearing joint replacements and in vitro evaluation of their biological impact.

Objectives

The objectives are as follows.

- To engage with the international community of stakeholders involved in the evaluation of human joint replacements and to inform them of the new protocols for the isolation of wear particles from low wearing replacements and the in vitro evaluation of their biological impact through a structured Workshop;
- To receive critical input from experts and other stakeholders present at the Workshop;

- To review, and revise where appropriate, the protocols in the light of input received in order to produce draft CEN Workshop Agreement outputs;
- To receive further comments from experts and the wider joint replacement community on the draft documents and to prepare final versions for approval as CEN Workshop Agreement outputs. In view of the technical nature of the material addressed by the proposed CWA outputs, together with the fact that the documents will not deal with safety aspects, public consultations are considered to be unnecessary; and to
- To make information on the new CWA outputs widely available and to encourage their evaluation and use in order to provide the basis for new European standards in the area.

5. CEN Workshop programme

The Workshop duration is expected to be 10 months. The Workshop aims to deliver two CWA outputs provisionally entitled:

1. 'Novel Isolation Methods for Wear Particles, Produced in Joint Replacement Implants and Related Devices, Based on Density Gradient Centrifugation'; and

2. 'Tiered Toolkit Approach to Evaluating the Biological Impact of Wear Particles from Joint Replacements and Related Devices'

Work plan

The work plan is as follows.

Month	Activity
April 2017	Formal submission of draft Project Plan to the Workshop Secretariat and CCMC for publication on the CEN website and start of 30-day commenting period. Initial contacts with identified stakeholders.
May 2017	Announcement of the Workshop. Preparation of Kick-off meeting and initial preparation of the Workshop, responding to invitees and others requesting attendance at the Workshop.
June 2017	Workshop Kick-off meeting (web-based).
August 2017	Finalization of draft CWA outputs. Distribution of draft CWA outputs to confirmed attendees for initial review and submission of preliminary comments for consideration prior to and at the Workshop. Distribution of Workshop agenda and venue details.
September 2017	Workshop of three days duration, including, if necessary, overnight revision of the draft CWA outputs for further consideration on second/third days.
November 2017	Distribution of revised draft CWA outputs for 1 month comment
December 2017	Review of comments and incorporation into draft CWA outputs, distribution for approval (2 week review).
February/March 2018	Submission of CWA outputs to CCMC for publication

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Note: This is a provisional work plan only and dates might change throughout the course of the project.

6. Workshop structure

The Workshop will be launched at a web-based Kick-off meeting at which the Project Plan will be approved and the Workshop Chairperson will be confirmed. This will be followed by one physical Workshop meeting of stakeholders lasting for three days (see work plan above). Draft documents for consideration at the Workshop will be distributed to the confirmed attendees prior to the Workshop and comments invited.

During this three-day Workshop, the draft CWA outputs will be presented and subjected to critical review and comment by those present. Comments/proposals for change will be addressed and incorporated into the documents, where appropriate. The revised CWA outputs will then each be submitted to a one month review, run in parallel, in which all registered Workshop participants will be invited to participate. Comments received during these reviews will be considered for inclusion in the final versions of the CWA outputs.

The final CWA outputs will then each be subjected to a two week review (run in parallel) amongst registered Workshop participants. The final Workshop outputs will be submitted to CCMC for acceptance and publication.

Chairperson

The Workshop Chair is responsible for ensuring the development of the CWA outputs respects the principles of the adopted Project Plan and the requirements of this document. The Workshop Chair will be confirmed at the Kick-off meeting.

The proposed Chair of the Workshop is Professor Joanne Tipper, University of Leeds.

Secretariat

In accordance with the CEN/CENELEC Guide 29 'CEN/CENELEC Workshop Agreements'[1], the Secretariat of the Workshop shall be held by a CEN National Member.

The proposed Secretariat for the Workshop is the British Standards Institution.

The Workshop Secretariat will provide the support needed to implement the Workshop.

Project team

[1] ftp://ftp.cencenelec.eu/EN/EuropeanStandardization/Guides/29_CENCLCGuide29.pdf.

The Workshop Project Team will revise the draft CWA outputs on behalf of the registered Workshop participants. It will be led by the Workshop Chair and will comprise two further members of the LifeLongJoints consortium: Dr Saurabh Lal, Research Fellow at University of Leeds responsible for method development of both new protocols; and Dr Peter Hatto, leader of Task 6.4 'Foundational work for Standards Development', who has wide experience of standardization activities in both CEN and ISO.

Registered participants

The registered Workshop participants will review and approve the work of the Project Team.

7. Resource requirements

All costs related to the participation of interested parties in the Workshop's activities will be borne by the interested parties themselves. Workshop services, provided by the Secretariat, will be met from the LifeLongJoints budget for the preparation of two CEN Workshop Agreements, as will the costs of the Chair and the LifeLongJoints consortium member(s) responsible for managing the technical aspects of the process. No additional support will be necessary or sought.

8. Related activities, liaisons, etc.

The subject matter of the Workshop comes within the scopes of two CEN Technical Committees: CEN/TC 285, *Non-active surgical implants*; and CEN/TC 206, *Biological and clinical evaluation of medical devices*. These two committees work closely with ISO/TC 150, *Implants for surgery* and ISO/TC 194, *Biological and clinical evaluation of medical devices*, respectively, and neither CEN committee has been responsible for the independent development of any documents that are not EN ISOs developed under the Vienna Agreement with an ISO lead. However, not all documents developed by the ISO committees have been adopted as EN ISOs. In particular, ISO 17853:2011, *Wear of implant materials – polymer and metal wear particles – Isolation and characterization*, has not been adopted by CEN/TC 285 and that committee currently has nothing in its work programme related to the proposed CWA output on wear particle isolation. Similarly, neither CEN/TC 206 nor ISO/TC 194 currently have deliverables related to the proposed CWA output on biological impact of wear particles in their work programmes. Hence, whilst the membership of both CEN/TC 285 and CEN/TC 206 will be invited to attend the Workshop, as will members of ISO/TC 150/SC4 and ISO/TC 194, given the respective timescales for the development of CWA outputs and formal standards, it is not deemed necessary to establish formal liaison with either CEN TC. However, in accordance with CEN Guide 29, the Workshop will report regularly to both CEN TCs, highlighting the most important issues and any possible conflicts that arise.

When published, in accordance with CEN Guide 29, a copy of each CWA output will be submitted to the respective CEN committee 'for assessment, with a view to possible transformation into a European Standard or other CEN/CENELEC deliverable'.

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9. Copy and exploitation rights

The copyright in the resulting CWA output shall be exclusive to CEN.

The CEN National Member providing the Workshop Secretariat shall be primarily responsible for its publication and distribution, in accordance with its own policies. Other CEN National Members may also distribute the CWA output at their own discretion and in accordance with their own policies.

All exploitation and distribution of the resulting CWA outputs shall be in accordance with CEN-CENELEC Guide 10: *Guidelines for the distribution and sales of CEN-CENELEC publications*[2].

10. Contact points

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[2] ftp://ftp.cencenelec.eu/EN/EuropeanStandardization/Guides/10_CENCLCGuide10.pdf.