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Clinical Investigation Plan (CIP) V1.4

Computed tomography to Rebut the myth that Easter and Christmas Hollow chocolate figurines are reused and are Edible safely (CRECHE)

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1. Background

In Germany and probably also in other European countries celebrating Easter and Christmas, it is a widespread urban myth that unsold chocolate Easter Bunny figures are reused, repackaged in seasonal foil and be offered again as chocolate Santa Clauses (and vice versa).

The Federal Association of the German Confectionery Industry (BDSI) repeatedly denies this accusation (see https://www.confectionerynews.com/Article/2013/04/16/Chocolate-santas-made-from-Easter-Bunnies-denials), as food hygiene legislation prohibits the reuse of already delivered products. Since chocolate Easter Bunnies and Santa Clauses are typical gifts for health care professionals as well as for inpatients, screening methods are necessary to ensure they do not contain any potentially harmful food components. Expired chocolate can "bloom" due to the aging of cocoa fat and sugar - this can be seen in a gray or white surface film. Hitherto, there is no evidence that (accidental) consumption of expired chocolate would be significantly harmful, but the likelihood of food intoxication in health care facilities, specifically hospitals, for the benefit of patients and medical staff must be kept to an absolute minimum. Unpacking all goods first to determine their edibility, and possibly repacking them after a visual or even gustatory check is practically impossible in everyday clinical practice.

Researchers from Manchester showed in March 2018 that computed tomography (CT) with the possibilities of three-dimensional (3D) reconstruction is a suitable imaging tool to reveal the complex structure of (seasonal) sweets such as chocolate Bunnies, Kit Kat® or Ferrero Rocher® (https://www.cnet.com/news/easter-chocolates-look-gross-in-xray-computer-3d-scans/). So far, however, these results have not been published in a peer-reviewed scientific journal. The morphometric characteristics of seasonal (i.e., Easter and Christmas) chocolate figures may suggest whether they came from the previous holiday season and were recycled. The outer and inner shape of the figurines is of course only one of many possible surrogates for recycling. Unsold chocolate could also have been melted and moulded again. To determine this, however, food chemical methods are required to determine the degree of degradation and the age of ingredients. Identical hollow chocolate bodies may be used for Santa and Easter Bunny figures, which only differ in their foil packaging.

While it appears to be unlikely, simply because of the logistical effort and considerable costs, that chocolate Santa Clauses consist of chocolate Easter Bunnies from the previous season, the urban myth has neither been scientifically proven nor refuted. Health care facilities, especially hospitals, must safeguard food hygiene and prevent staff and patients from inadvertently consuming potentially harmful edibles.

2. Hypotheses and Objectives

We postulate that

1. Assumptions as to which chocolate Easter Bunnies are repackaged as Santa Clauses for resale represent an urban myth,
2. Low-dose CT imaging is a fast and reliable screening tool for depicting the inner shapes and contours of seasonal chocolate hollow figurines.

In the event of strong similarity or correspondence between Santa Claus and Easter Bunny figures from the same manufacturer, it cannot be excluded that the products are reused and should at least be enjoyed with caution. In case of clear differences between the figures, however, this would refute the described modern legend.

In the absence of reliable prior information, this investigation is carried out in an exploratory fashion. The researchers do not pose a confirmatory null hypothesis.

Primary and co-primary objectives are:

1. To describe CT-morphological features of the internal structure of chocolate Easter Bunnies and Santa Clauses from various manufacturers.
2. To quantify the average and maximum chocolate layer thickness of the entire figure and its base.
3. To compare the appearance of chocolate Easter Bunnies Santa Clauses based on CT data by blinded assessment of different examiners.

Secondary objectives are:

1. A food chemical analysis of chocolate Santa Claus figurines to determine the age of ingredients and any hints towards food recycling in collaboration with a university expert partner (*requested: Institute for Food Technology and Chemistry, Technical University Berlin, Germany*)
2. To anonymously assess the strength of agreement with five study-relevant statements using a Likert scale by 100 randomly selected volunteers at either trial site, based on the customized GRINCH (Generic Risk Items Noted by Chocolate-consumers in Health-care settings) 5-item questionnaire.

The CRECHE examination will be conducted at the institutes for radiology of the BG Klinikum Unfallkrankenhaus Berlin gGmbH, Berlin, Germany, and the BG Klinikum Duisburg, Duisburg, Germany, which have long-standing expertise in CT imaging, including experimental methods, three-dimensional image reconstruction and processing, etc.(1-8) In addition, trained study staff is available for interviews and survey, data entry and management.

3. Inclusion and exclusion criteria

Commercially available chocolate Easter Bunnies of any size, shape and from any manufacturer will be included, which were purchased by the trialists before, during and immediately after the Easter celebrations in 2020. Also included will be chocolate Santa Claus figurines of

every size, shape and from any manufacturer, to be purchased by research team members beginning with their availability in stores (presumably from September 2020 onwards). Individually manufactured or other special chocolate sculptures will be excluded.

After the first availability of seasonal chocolate treats, i.e., in the 40th calendar week (from Monday, September 28th, to Friday, October 2nd, 2020, between 8:00 a.m. and 4:00 p.m.), 100 randomly selected volunteers passing the general entrance areas of either trial site will be approached by study assistants and asked to answer the anonymous GRINCH questionnaire (see Appendix 1). For practicality reasons, this will be done in a paper-based fashion. Protective measures to prevent spreading of SARS-CoV-2 / COVID-19 (i.e., face masks, minimum distance of 1.50 m, and hand disinfection with alcoholic solutions) will strictly be maintained. The poll will therefore not take place in the waiting area of the emergency department or within the hospital. Questionnaire answers will be transferred into the electronic data capture (EDC) system by study assistants.

4. Interventions

4.1. Measures

Chocolate figurine will be gauged physically without removing their foil jacket (i.e., maximum height, width and depth, and maximum circumference taken by a tape measure, weight determined on a kitchen scale). After generation of an ID and database acquisition, native whole-body computed tomography (WBCT) will be carried out on last-generation scanners under defined conditions.

In accordance with the ALARA (as low as reasonably achievable) principle of radioprotection, a low-dose CT protocol derived from CT studies of the thorax was adapted for this study. Scans will be performed using 128-row multi-slice detector scanners (Definition AS+, Siemens, Germany) according to the following imaging protocol:

- Fixed tube voltage of 80 kVp
- Adapted tube currents regulated by a real time dose modulation software (CARE Dose 4D, Siemens, Germany) of ~ 9 mAS
- Collimation (cSL) of 0.6
- Rotation time (Ti) of 0.3 sec

Images will be reconstructed in 2 mm slices in axial, coronal, and sagittal planes with a standard kernel. Volume rendering techniques will be applied for 3D imaging using postprocessing software (ISP Portal, Philips, Netherlands or Syngo.Via, Siemens, Germany).

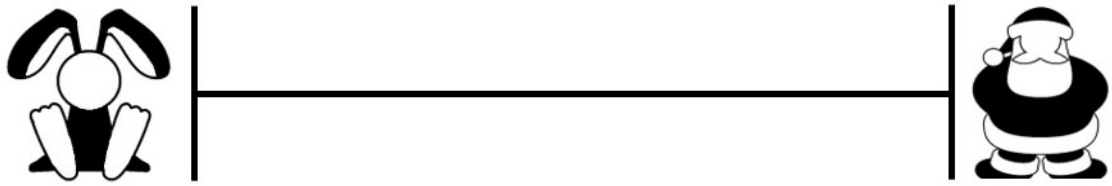
All images are stored in the Picture Archiving and Communication Systems (PACS) of the trial sites for further processing and diagnosis. In an Electronic Data Capability (EDC) system, manually collected information such as season, manufacturer, expiry date, best before date, weight, height, width, depth, and maximum size of the figures are stored. Radiological indices include the maximum height, width, and depth of the overall figure, as well as average and maximum chocolate layer thicknesses. Measurements are made on the floor, at the top and on the side walls of the figure in all three dimensions. Various approaches to automated image analysis were examined in preliminary examinations which proved unreliable. Thus, manual measurements and surveys will apply to this project.

After examination, objects will be stored at fridge temperatures of ° C before shipped to the TU Berlin for food chemical analysis.

4.2. Comparisons

The radiological contours and 3D surface reconstructions of chocolate figurines from the same manufacturer will be rated independently by three board-certified radiologists, blinded to the brand and type of seasonal article, using a 10-cm visual contour resemblance scale (CRS), whether they are more like an Easter Bunny or a Santa Claus (Fig. 1).

Fig. 1 Contour-Resemblance Scale (CRS).



4.3. Anonymous poll and interview

We scrutinized the most recent Eurobarometer survey on food safety (https://www.efsa.europa.eu/sites/default/files/corporate_publications/files/Eurobarometer2019_Food-safety-in-the-EU_Full) as well as tools like the validated Chocolate version of the Food Cravings Questionnaire(9) to design the anonymous interview form for this study. However, current instruments appeared to be to extensive (i.e., up to 90 items) or beyond the scope of our study. We therefore created the simple GRINCH (Generic Risk Items Noted by Chocolate-consumers in Health-care settings) instrument with 5 Likert scale-based items, which we think corresponds well to the objectives of our research project. We will aim for assessing the internal consistency of the instrument by factor analysis.

5. Sample size estimation and biostatistics

No formal sample size calculation was employed for this study. Trialists had bought chocolate Easter Bunnies from various manufacturers in supermarkets and in retail stores without prior consultation during the 2020 Easter season. Items will be sorted and categorized according to their size and shape. Doubles will be kept as a reserve.

A similar procedure is planned for the (pre-)Christmas season 2020 (presumably starting in early September 2020). A total of 20 Easter Bunny and Santa Claus figurines of different sizes from well-known and / or common manufacturers will be included. This sample will guarantee both unproblematic CT examination flows as well as sufficient variance for quantitative analyzes. Statistical analysis will be performed at the Center for Clinical Research (zkf) of the BG Klinikum Unfallkrankenhaus Berlin gGmbH. Descriptive statistics include proportions, percentages, means, standard deviations, medians, interquartile ranges, ranges, and confidence intervals (CI). Interobserver correspondence between different observers is determined after situation-specific data transformation using the intraclass correlation coefficient (ICC) and

visualized in the form of scatter diagrams. CRS scales ´will be compared graphically in a forest plot format. Depending on the sample size, CRS values averaged over observers will either be regarded quasi-normally distributed and evaluated by a t-test, or, in case of skewed and / or non-normal distribution analysed by the Wilcoxon-Mann-Whitney test. Questionnaire surveys will be handled in a similar fashion.

Due to the non-confirmatory nature of the study, p-values and confidence intervals must only be interpreted in an exploratory manner.

Commercial software packages like SPSS V25.0 and STATA V16.0 for Windows will be employed for all computations.

6. Trialists' remarks

This investigation has humorous features. Results are attempted to be published in the upcoming or next year's Christmas issue of the *British Medical Journal*, which traditionally contains articles with an ironic view of the (clinical) research landscape. The almost legendary citation is the lack of randomized trials for jumping from a great height with and without a parachute(10) found by a systematic review, but also studies on national myths and inappropriate acronyms(11, 12) were published there. Chocolate treats were last studied in 2013 with the question of the differential survival time of chocolate products from two common manufacturers offered on a hospital ward(13).

The applicants guarantee strict compliance with scientific and ethical standards such as ICH-GCP, data protection in accordance with EU-GDPR, professional statistical evaluation of results and reporting in accordance with EQUATOR recommendations. This project will prospectively by registered in the CurrentControlledTrials registry. **No individual or personal human data will be collected, recorded, processed, or stored.** Diagnostic radiation will only be applied to inanimate objects which will not be released for consumption after examination.

7. Literature

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8. Appendix

GRINCH (Generic Risk Items Noted by Chocolate-consumers in Health-care settings) 5-Item-Questionnaire for anonymous polling of volunteers.